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LIPOIDGRANULOMATOSIS (TYPE, HAND-SCHÜLLER-CHRISTIAN)

REPORT OF A CASE

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Rowland [1] in 1928 collected twelve instances of a disease described under various titles in the literature and characterized by the symptom complex of defects in the membranous bones, exophthalmos and diabetes insipidus. He entitled the disease "Schüller-Christian's syndrome." To these he added two striking cases of his own, one of which was studied post mortem. Hand [2] in 1893, under the title of "Polyuria and Tuberculosis," described this symptom complex in a boy of 3 years who, in addition to exophthalmos and polyuria, showed at necropsy yellow nodules in the defects in the internal and external tables of the skull, grayish nodules in an enlarged liver and enlargement of the spleen. Only the nodules in the liver were studied microscopically; they revealed chronic inflammatory granulation tissue. In the absence of significant criteria, the condition was named in the pathologic report tuberculosis, although syphilis was also considered. The author noted, however, that he believed the lesion was neither that of tuberculosis nor that of syphilis. Kay in 1905 reported an instance of "acquired hydrocephalus with atrophic bone changes, exophthalmos and polyuria" in a boy of 7 years, which he ascribed to a tumor at the base of the brain. Schüller [3] in 1915 described two cases, in an article entitled "A Peculiar Syndrome of Dyspituitarism." The first was that of a girl of 3 years with the same symptom complex. He thought the condition was due to a disturbance of the pituitary gland. In the second instance, the patient suffered, in addition, from dystrophia adiposo-genitalis. Schüller attributed the condition to a tumor at the base of the brain.

From the Medical Service of Montefiore Hospital.

1. Rowland, R. S.: Arch. Int. Med. **42**:611, 1928.

2. Hand, A.: Arch. Pediat. **10**:673, 1893; Am. J. M. Sc. **162**:509, 1921; Proc. Philadelphia Path. Soc. **16**:282, 1891-1893.

3. Schüller, A.: Wien. med. Wchnschr. **71**:510, 1921; Fortschr. a. d. Geb. d. Röntgenstrahlen **23**:12, 1915-1916; Brit. J. Radiol. **31**:156, 1926.

Christian [4] in 1919, under the title, "Defects in Membranous Bones, Exophthalmos, and Diabetes Insipidus—An Unusual Syndrome of Dyspituitarism," reported the case of a girl of 5 years. None of the cases except that of Hand came to autopsy. The other authors ascribed this unusual symptom complex to dyspituitarism or to a tumor at the base of the brain. In view of the apparent historical priority it has been suggested [5] that this symptom complex be designated as Hand's disease.

Subsequently, instances of this disease were reported by numerous investigators. The literature to 1930 has been reviewed by one of us in a previous article,[5] and to 1931, by Moreau.[6] Further instances have been described by Chiari,[7] Sosman,[8] Frumann-Dahl and Forsberg,[9] and Ighenti.[10]

Sosman mentioned that several instances have been reported [11] in which the symptom complex of Hand's disease was present and, in addition, an involvement of the cranial bones which was similar roentgenologically to osteitis fibrosa. In a previous communication [5] were reported changes in the vertebrae, found roentgenologically, which on microscopic examination proved to be similar to those found in osteitis fibrosa (*zusammengesetzte Bälkchen* of Freund).[12]

The observations in the cases studied anatomically are listed in table 1. In an earlier publication,[5] two cases of disturbed lipoid metabolism that came to autopsy were described, and it was concluded that in these cases, as well as in all the allied cases of Hand's disease, the basic lesion was a chronic, noninfectious, abacterial, inflammatory granuloma due to the deposition of various lipoid substances in the involved tissues. This lesion was termed "lipoidgranuloma," and it is believed

4. Christian, H. A.: Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, Contributions to Medical and Biological Research, New York, Paul B. Hoeber, Inc., 1919, vol. 1, p. 390.

5. Chester, W.: Virchows Arch. f. Path. Anat. **279**:561, 1930.

6. Moreau, J.: Arch. franco-belges de chir. (supp.) **32**:697, 1931.

7. Chiari, H.: Ergbn. d. allg. Path. u. path. Anat. **24**:396, 1931.

8. Sosman, M. C.: Am. J. Roentgenol. **23**:581, 1930; J. A. M. A. **98**:110, 1932.

9. Frumann-Dahl, J., and Forsberg, R.: Norsk mag. f. lægevidensk. **92**:523, 1931; abstr., J. A. M. A. **97**:820, 1931.

10. Ighenti, W. K.: Virchows Arch. f. path. Anat. **282**:585, 1931.

11. Schoen, R.: München. med. Wchnschr. **71**:1713, 1924. Heard, J. D.; Schumacher, F., and Gordon, W. B.: Am. J. M. Sc. **171**:38, 1926. Sophian, A.: J. A. M. A. **95**:483, 1930. Slauch, A., and Donalies, H.: Med. Klin. **26**:459. 1930.

12. We are at a loss, as is the author himself, to interpret Wassiljeff's case. It can hardly be termed a case of Hand's disease, though the osteosclerotic process in the bones may well be subsequent to lipoid deposits.

TABLE 1.—*Recorded Cases of Lipoidgranulomatosis (Hand-Schüller-Christian Type) with Observations at Necropsy*

Author	Date	Age of Patient	Sex	Diagnosis	Pathologic Observations	Interpretations
Hand.....	1893	3	M	Polyuria and tuberculosis	Yellowish granulation tissue in the cranial bone defects, liver, spleen and lymph nodes	Because lesion was not characteristic of syphilis a diagnosis of tuberculosis was made. Author did not believe the pathologic process could be attributed to tuberculosis
Hochstetter and Veit	1922	44	M	Multiple sclerosis of the endocrine glands	Granulation tissue in skull, femur, pituitary gland, dura, hili of kidneys, lungs, eyelids	Chronic inflammatory granulation tissue
Wiedman and Freeman	1924	9	M	Xanthoma tuberosum: two necropsies disclosing lesions of central nervous system and other tissues	Granulation tissue containing lipoid substances found in skin, liver, lung, pleura, skull, dura, pineal gland, pituitary gland, hypothalamic region	The lesions in the liver were due to syphilis with secondary inflammatory granulation tissue
Schutz, Wermbter and Puhl	1924	2	F	Granuloma-like systemic disease of the hematopoietic apparatus	Granulation tissue in cranial bone defects, long bones, vertebrae, ribs, spleen, lungs, liver, lymph nodes, pancreas, myocardium	A true granuloma—chronic infectious inflammatory granulation tissue
Thompson, Keegan and Dunn	1925	9	M	Defects of membranous bones, exophthalmos and diabetes insipidus	Inflammatory granulation tissue in skull, pelvis, femurs, scapulae, clavicles, ribs, cervical and lumbar vertebrae, tuber cinereum, infundibulum, dura, lungs	The lesion was inflammatory or infectious rather than of degenerative or metabolic etiology
Kyrklund.....	1926	12	M	A rare syndrome (cranial softening, exophthalmos, adiposogenital dystrophy, diabetes insipidus)	Granulation tissue in skull, scalp, dura, hypothalamic region, kidney	A tumor of sarcomatous nature
Rowland.....	1928	5	M	Xanthomatosis and the reticulo-endothelial system	Granulation tissue containing lipoid substance found in cranial defects of skull, pituitary gland, ilium, vertebrae, lungs, thyroid gland, lymph nodes, heart, kidney	A peculiar granuloma due to deposition of lipoid substances subsequent to a metabolic disturbance
Herzenberg.....	1928	5	M	Niemann-Pick's disease	Granulation tissue containing lipoid substances in cranial defects of skull, sternum, femurs, vertebrae, pituitary gland, infundibulum, thymus tonsils, lymph nodes, spleen, liver, skin	Chronic granuloma due to deposition of lipoid substances; constitutional anomaly causing disturbance in lipoid metabolism with formation of a chronic granuloma due to the deposition of lipoid
Schüller and Chiari	1931	29	M	Xanthomatosis	Granulation tissue containing lipoid substances in cranial defects of skull, femur, ilium, psoas, lids, pleura, lungs, hypothalamic region	Chronic inflammatory granuloma due to disturbance in lipoid metabolism
Henschen.	1931	3	F	Christian syndrome	Xanthomatous changes in bone marrow of tibia, ribs, pelvis; retroperitoneal fat and loose connective tissue all over the body, spleen, lymph nodes, liver	Granulomatous lesion due to disturbance in lipoid metabolism
Ighenti.....	1931	3	M	General granulomatous xanthomatosis	Granulomatous xanthoma tissue in cranial defects of skull, pelvic bones, lymph nodes, liver, colon, ileum, duodenum, spleen, lungs, tonsils, tongue, skin, dura, stomach, fat about hili of kidneys	Granulomatous lesions due to disturbance in lipoid metabolism

to be as characteristic for this disease as the gumma and tubercle are for syphilis and tuberculosis.

This granuloma has three main constituents: (1) the characteristic foamy lipoid cell, the specific element that contains the lipoid substances; (2) the inflammatory cellular exudate, a response of the tissues to the lipoid substances; (3) connective tissue proliferation.

It is the opinion of present investigators (Christian,[4] Chester,[5] Chiari [7] Ighenti [10]) that the lesion is essentially a disturbance in lipoid metabolism. To such a condition, the term xanthoma, meaning a tumor, is hardly applicable, and less so is the term xanthomatosis, meaning multiple tumors. For this reason it was suggested [5] that the lesion be termed "lipoidgranuloma," and the generalized form, "lipoidgranulomatosis."

REPORT OF CASE

History.—P. S., a Jew, aged 28, single, was admitted to the Neurological Division of Montefiore Hospital, May 8, 1928, complaining of (1) excessive thirst and frequent and excessive urination of eighteen months' duration, (2) a discharge from the left ear of thirteen months' duration, (3) a discharging anal fistula of ten months' duration, (4) a discharge from the right ear and a draining anus of the right thigh of four months' duration and (5) weakness and loss of weight.

The family history was irrevelant.

When the patient was 8, he had an uncomplicated scarlet fever. At 13, he suffered a fall that resulted in laceration of the face and a fracture of the nasal bone for which operative interference was necessary to relieve the nasal obstruction. At 21, he had arthritis of the ankles and knees lasting two months. Between 16 and 24 he was in good health, working as a teamster. At the latter age, he weighed 210 pounds (95.2 Kg.).

A series of symptoms and operative procedures began at 23 that were to invalid him for the remainder of his life. Because of pain an upper right molar tooth was extracted, and in this area granulation tissue appeared. All the teeth in that section, as well as many in the lower jaw, began to loosen and fall out. Within two years he had lost most of his teeth; an operation for "multilocular cyst" of the jaw was followed by a partial resection of the lower jaw for "granuloma" of the jaw. The following year polydipsia and polyuria were first noted.

At 25, he was hospitalized on several occasions for attacks of dizziness and double vision, as well as for severe pains in the left side of the chest, interpreted as "dry pleurisy." At 27, chronic eustachian salpingitis was followed by chronic otitis media in turn complicated by right mastoiditis, for which mastoidectomy was performed. Because of pain on defecation and a "yellowish" rectal discharge, he was twice operated on for fistula *in ano* and rectal abscess. Shortly thereafter he complained of severe pain in the right thigh and, as a roentgenogram revealed areas of bone absorption in the upper part of the right femur, he was operated on for osteomyelitis. About six months prior to his admission to Montefiore Hospital, a course of injections of pituitary relieved his polydipsia and polyuria considerably.

Biopsies on tissue removed from several of the sites operated on (mandible, mastoid and femur) resulted in a report of a "peculiar type of granuloma."

Physical Examination.—The patient was revealed as a fairly well developed adult man weighing 165 pounds (74.8 Kg.), obese despite the history of loss of weight. The skin was coarse, dry and of a pseudomyxomatous consistency. The

absence of perspiration, even in hot weather, was striking. There was a striking absence of facial hair; that of the axilla was sparse, and there was a typical female distribution of the pubic hair. Large pads of fat were present in the gluteal region.

Scars of the sites operated on were noted, with persistent draining sinuses in the mastoid, perineal and thigh areas. A purulent discharge was present in both ears, accompanied by pain in both ears and deafness in the left. The old fracture of the nasal bone and the depressed septum caused moderate nasal obstruction. The lower jaw was markedly foreshortened; most of the mandible had been resected. Only two upper teeth remained. Pyorrhea alveolaris was marked, and speech and deglutition were impaired.

There was tenderness of bones over the left side of the chest. The heart and lungs were without abnormality except for a persistent bradycardia (blood pressure, 110 systolic and 80 diastolic). The liver and spleen were not palpated. There were no abdominal masses. There was no edema of the lower extremities. Walking was difficult; genu valgum was present.

The appetite was poor, and there was habitual constipation. For the past several months the intake of fluids ranged from 6 to 12 liters, and an equivalent amount of pale watery urine was voided. At times urine was voided as frequently as every twenty minutes.

The clinical impressions at that time were: (1) pituitary dyscrasia; (2) diabetes insipidus syndrome; (3) bilateral chronic otitis media with mastoiditis; (4) chronic osteomyelitis of the right femur, probably tuberculous; (5) chronic fistula *in ano,* probably tuberculous.

Clinical Course.—May 21, 1928: Roentgenograms of the skull revealed an area of bone absorption in the parietal region (fig. 1 *a*) and an almost complete absence of the mandible (*b*). The sella turcica (*c*) showed no abnormalities. Roentgenograms of the right femur showed areas of bone destruction and production in the proximal portion. There was a large defect in the right wing of the sacrum. A "malignant granuloma" with metastases to the skeletal system was considered.

May 30, 1928: With administration of pituitary, 1 cc. daily, the intake of fluids was reduced from 2,700 to 3,800 cc., with a corresponding output.

June 13, 1928, to March 18, 1930: Roentgen therapy (Dr. Lenz) was begun as a palliative measure. Eventually radiation was applied to six skull fields, the right femur, the perineal field, both ears, the lower part of the left axilla, and the lower part of the right side of the chest, with a total of 23 erythema doses.

Sept. 17, 1928: The hearing in the right ear and the pain in the right parietotemporal region were found greatly improved since the roentgen therapy.

Oct. 10, 1928: Rectal examination revealed a granulomatous perianal ulceration extending to the internal anal sphincter. A specimen of tissue taken for biopsy was reported on as chronic granulation tissue. A roentgenogram showed extension of the skull involvement.

Feb. 11, 1929: The diabetes insipidus syndrome was being well controlled with injections of pituitary. At this time it was suggested that there was involvement of Rathke's pouch with extension to the tuber cinereum.

April 13, 1929: A biopsy of the site of the previous biopsy in the axilla, which had failed to heal, showed a peculiar type of granuloma in which there were large oval cells with lipoid material in the cytoplasm.

April 20, 1929: The left external auditory meatus was completely blocked by granulations. Chronic otitis media was noted on the right side, but the hearing was improved and the discharge lessened.

June 13, 1929: There was tenderness over the ribs from the angle of the scapula to the twelfth rib in the posterior axillary line.

Aug. 23, 1929: Actinomycosis or a low grade pyogenic infection was suggested as an etiologic factor. The general condition was good. The weight was 205 pounds (95 Kg.)

Sept. 19, 1929: The gain in weight and the loss of libido in a patient with dystrophia adiposogenitalis and diabetes insipidus suggested a lesion in or about the hypophysis. Perimetric examination showed concentric restriction of both visual fields plus a relatively greater limitation in the upper part of the temporal field on the left.

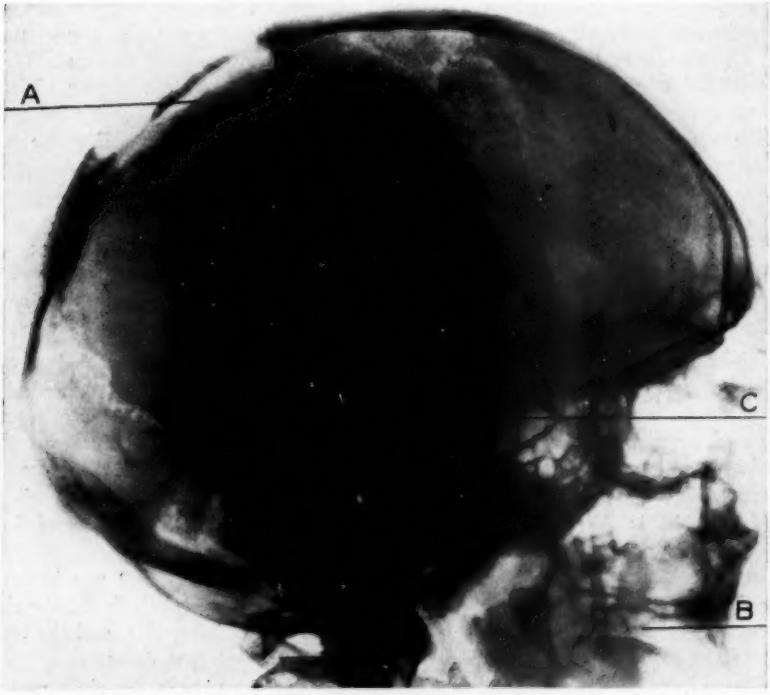

Fig. 1.—A roentgenogram of the skull showing a large defect in the parietal bone (*a*), absence of the mandible (*b*) and a normal sella turcica (*c*).

Jan. 29, 1930: A "sticking pain" was felt in the lower part of the occipital region as well as in the ankles and the right side of the chest. Nervousness, dizziness, vomiting, faintness, tachycardia, polydipsia and polyuria occurred when pituitary was not given.

May 21, 1930: Roentgen therapy had been applied to the region of the pituitary gland since Feb. 20, 1930. There were noted a gain in weight (212 pounds [96.1 Kg.]), a restoration of virility, an occasional stabbing sensation in the proximal part of the right femur and pain in the chest. An occasional sinking sensation was relieved by bringing up thick, yellowish sputum. The sinuses had stopped discharging. The symptoms of diabetes insipidus were controlled with pituitary. It was deemed advisable to continue roentgen therapy.

July 7, 1930: There was cloudiness of the left antrum.

Aug. 22, 1930: The left antrum was cloudy, with an irregularity of the medial wall of the sinus, probably due to bone involvement.

Oct. 22, 1930: The edge of the liver was palpable.

Dec. 10, 1930: Progressive weakness, awkwardness, tremor of the hands and shuffling gait were noted. The patient no longer showed response to irradiation. An exploration of the pituitary gland was deemed inadvisable because of widespread metastases.

Jan. 8, 1931: The patient was discharged with the diagnosis of (1) chronic granuloma involving the jaw, skull, mastoid process, proximal end of the right femur, sacrum and perianal region, (2) diabetes insipidus and (3) Frölich's syndrome.

Jan. 13, 1921: The patient was readmitted, complaining of weakness in the knees, inability to walk, blurred vision, unsteady gait and generalized tremor. The neurologic examination showed generalized weakness, definitely more on the right than on the left, and inconstant ataxia in the upper extremities, the tremor being more marked when pituitary was withdrawn. There were also ankle clonus

TABLE 2.—*Blood Counts*

	May 13, 1928	Sept. 12, 1929	Feb. 16, 1931
Hemoglobin	75%	.....	62%
Platelets	.....	.....	450,000
Red blood cells	4,600,000	.....	3,100,000
White blood cells	8,800	10,000	10,800
Polymorphonuclears	72%	72%	76%
Lymphocytes	20%	23%	17%
Mononuclears	7%	....	2%
Basophils	1%	1%	...
Eosinophils	...	2%	5%

on the right, an equivocal Babinski sign, Hoffmann's sign on the right, and concentric restriction of the visual fields. There were sensory disturbances in the left trigeminal area, which might have been due to an old peripheral lesion of the facial nerve or to involvement of the gasserian ganglion. The neurologic consultants thought that these findings indicated an extension of the pathologic process to the adjacent portions of the cerebral hemisphere on the left.

Jan. 31, 1931: The diagnosis of Hand's disease (Schüller-Christian syndrome) was made. It was thought that the entire clinical picture could be explained by lipoidgranulomatous infiltrations of the hypophysis and the hypothalamic region, causing dystrophia adiposogenitalis, diabetes insipidus and extensive osteoclastic skeletal changes with involvement of the skull, alveolar process of the maxillary bone, mandible, mastoid process, proximal end of the right femur, sacrum and ninth rib on the left.

Feb. 8, 1931: An osteoclastic defect was revealed in the proximal portion of the left tibia.

March 3, 1931: The patient's condition had become progressively worse. The profound asthenia was unusually striking. He died on March 4, 1931, of what was considered to be hypostatic pneumonia.

Laboratory Data.—The blood counts are shown in table 2. The bleeding time was 5¼ minutes; the coagulation time, 9⅔ minutes; the

clot reaction time, 3 hours. The result of the tourniquet test was negative. The blood icteric index was 6. The result of the van den Bergh test was normal. In a congo red test, 85 per cent of the dye was retained in the blood stream after one hour. The blood chemistry was as follows: urea nitrogen, 7.7 mg. per hundred cubic centimeters; cholesterol, 152 mg.; calcium, 9.8 mg.; phosphorus, 3.9 mg.; total fat, 1.71 per cent; serum proteins, 7.49 per cent; albumin, 4.71 per cent, and globulin, 3.23 per cent.

The Wassermann test of the blood and that of the spinal fluid gave negative results. The spinal fluid was normal. The spinal fluid fat was 12 mg. per hundred cubic centimeters; the protein, 42.8 mg. The sputum showed no tubercle bacilli or other micro-organisms. The urine was normal and showed no Bence-Jones protein. A complement-fixation test for B. mallei was negative.

A sugar tolerance test on Jan. 16, 1931, yielded results as follows: fasting, 89 mg. per hundred cubic centimeters; one hour after the administration of 100 Gm. of dextrose, 110 mg.; two hours after, 86 mg. A test made on Nov. 15, 1929, gave the following results: fasting, 87 mg.; one-half hour after the administration of 100 Gm. of dextrose, 114 mg.; one hour after, 77 mg., and two hours after, 79 mg.

The basal metabolism was plus 1 per cent in the first determination and minus 4 per cent in the second. An electrocardiogram showed left axis deviation and sinus bradycardia.

Autopsy (Dr. David Perla).—The body was that of an obese young man, the general configuration, deposition of fat tissue and distribution of pelvic hair as in dystrophia adiposogenitalis. The skin was smooth, dry and pale. On the face was a linear scar extending from the left nostril to the frontal bone in the midline. The lower half of the mandible was absent, and there was a deep transverse scar across the chin. Only two of the upper teeth were present; the contiguous tissue was pale and yellowish on section. Deep scars were present in the left axilla and over the proximal portion of the right femur. There was pitting edema of the lower extremities.

Significant changes were present in the lungs, pituitary gland, osseous system and testicles.

Lungs: The lungs were grayish red and contained air throughout. The pleura was slightly thickened. Besides small patches of bronchopneumonia in both lower lobes, the cut surface showed numerous small, irregular yellow nodules varying from 0.5 to 2 cm. in size. Within these areas were small yellow spots from which grayish strands extended into the surrounding tissue. The pulmonary vessels appeared normal. The bronchi were congested.

Pituitary Gland: The pituitary gland was slightly enlarged, and on section was grayish white. The capsule was thickened.

Osseous System: The calvarium showed a large punched-out area about the size of a small plum in the midportion of the parietal bone (fig. 1 *a*) extending from both sides of the longitudinal suture. The cortex was eroded, and both tables

were replaced by a dense membrane. The region of the sella turcica, the sphenoidal sinuses and the base of the skull showed no abnormalities. The frontal bones and the retro-orbital regions were normal.

The cut surface of the proximal portion of the right femur showed the cortex to be markedly thickened, almost entirely obliterating the medullary cavity for a distance of 3.5 cm. The medulla was there replaced by a grayish-white sclerosed tissue of the consistency of bone. Distal to this area, the medullary cavity contained fat marrow.

Several of the lumbar and thoracic vertebrae and ribs showed no gross abnormalities.

Testes: The testes were atrophic and on section consisted of dense fibrous tissue.

Other Organs: The thyroid gland showed a moderate amount of colloid and no abnormalities. The pancreas was firm and grayish yellow; it revealed no abnormalities. The right suprarenal gland weighed 9.5 Gm.; the left, 14.5 Gm. The cortex was narrow and contained the usual amount of lipoid. The medulla showed moderate postmortem autolysis. The heart weighed 440 Gm. It showed "tigering" of the right ventricle. The liver, spleen and lymph nodes showed no significant gross changes. These as well as the other organs are mentioned in the microscopic protocol.

Microscopic Observations.—The pleura was thickened as were the interlobular and alveolar septums, the latter often showing marked cellular infiltration. Numerous areas were edematous and congested and the alveoli filled with a conglomerate of large, vacuolated cells. These appeared to be proliferated, highly vacuolated, alveolar epithelial cells and were apparently different morphologically from the lipoid elements in the granulomatous tissue in other organs. The same plugs were seen in some of the smaller bronchi, about which there was some connective tissue proliferation with little cellular infiltration. With sudan III, these vacuolated areas stained from yellowish red to brown, very little of the sudanophilic substance refracting polarized light. With Smith-Dietrich stain there was little bluish-staining substance in this area. In some areas, pulmonary tissue was barely recognizable and was replaced by a granulomatous tissue consisting of fibrous connective tissue elements and a considerable number of lymphocytes and a few plasma cells. In a few areas there was an increase in perivascular connective tissue.

Pituitary Gland: The capsule was considerably thickened. At the junction of the lateral posterior portion of the anterior lobe and the posterior lobe was a large, fairly circumscribed nodule consisting of large, closely packed, polyhedral cells, lying in a meshwork of connective tissue fibers. These cells (fig. 2) had small, oval or round, darkly staining nuclei, rich in chromatin. Occasionally, vesicular reniform, and bizarre, irregularly formed nuclei were seen. With Mallory's trianiline stain the nuclei stained red. The cytoplasm was plentiful and honeycombed or foamy in appearance; occasionally, however, vacuolated forms were seen. The cell membranes were usually distinct, though occasionally rather indefinite because of the compactness of these cells. These lipoid cells (*Schaumzellen,* xanthoma cells) were also seen in isolated groups and even singly. A few fat cells were also seen in this nodule. The connective tissue proliferation (fig. 2*f*) seemed to be in inverse ratio to the number of lipoid cells, so that in some areas the connective tissue elements and round cell infiltration predominated, and only an occasional lipoid cell was seen. In some areas the lipoid cells were absent and apparently replaced by dense, fibrous, fairly acellular connective tissue.

The anterior lobe (fig. 3) was at least twice normal size. The vessels were considerably dilated and filled to various degrees with cellular elements of the blood. The stroma (fig. 3*g*) showed two small, fairly dense areas of connective tissue fibers in the lateral portion of the anterior lobe, one on each side, containing numerous fibroblasts, a few small blood vessels distended with cellular elements, and groups of basophils in alveolar structure, in the centers of which were occasional chromophobe cells with greatly increased protoplasmic structure and large vesicular nuclei. There were also small areas of hemorrhage in these scarlike areas of connective tissue. The connective tissue gradually tapered out and became continuous with the rest of the stroma of the gland.

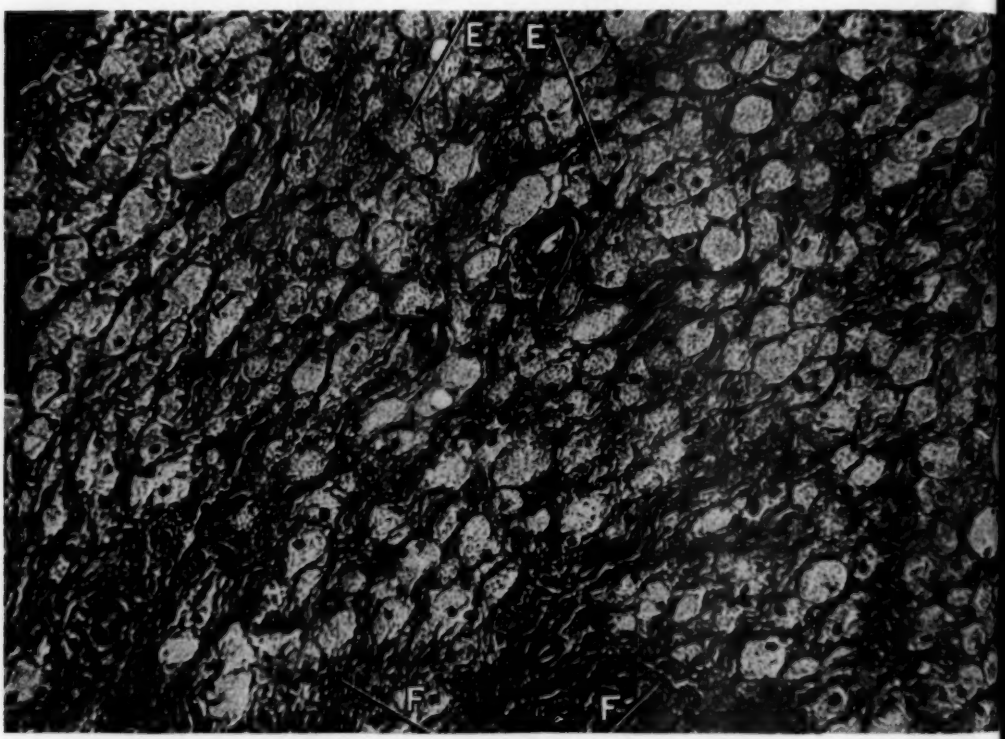

Fig. 2.—A lipoidgranuloma showing lipoid cells (*e*) and connective tissue proliferation (*f*).

The alveolar structure was preserved throughout. The eosinophils were greatly reduced in number and were irregularly and diffusely scattered throughout the anterior lobe, being found in greater numbers in the posterior portion. The nuclei were often eccentric and varied considerably in size. The protoplasm contained numerous coarse and fine eosinophilic granules. The cell membranes were distinct. The basophils, although most numerous in the anterior portion of the anterior lobe, were also found in large numbers throughout the rest of the lobe, as well as in large groups in the tissues between the anterior and posterior lobes. The basophilic foci were composed either of single alveoli or of groups of alveoli in which practically all the cells were of the large, heavily granulated, deeply staining basophilic

type (fig. 3*h*). Smaller varieties were seen in the so-called "pars intermedia." In the basophilic areas a distinct thickening of the stroma was noted. The nuclei were oval or slightly irregular and often eccentric and varied considerably in size. The cell membranes were distinct, the cellular configuration depending on the massing of the cells.

Diffusely throughout the anterior lobe, particularly in the lateral, posterior and central portions, either singly or in groups, at times forming complete alveoli, were numerous altered chromophobe cells (fig. 3*i*).

Occasionally, these cells were found in the center of an alveolus, the common sites of their precursors, the main cells, surrounded by basophils and eosinophils.

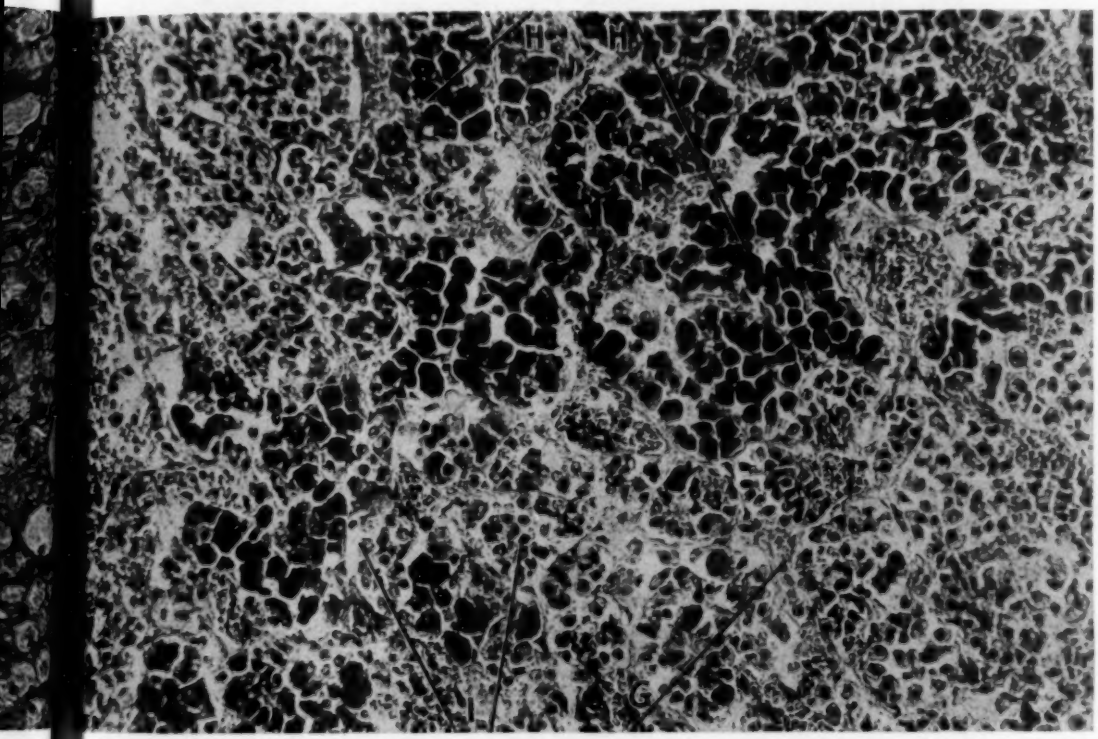

Fig. 3.—A section of the anterior lobe showing thickened stroma (*g*), alveoli formed of large basophils (*h*) and alveoli formed mainly of altered chromophobe cells (*i*).

The nuclei varied in size; they were round or oval, vesicular, and occasionally irregular in form with varying chromatin content. The protoplasm stained pale brown (hematoxylin and eosin), varied in amount, and was granular. There was no distinct cellular membrane; the nuclei often appeared to lie in small masses of protoplasm. The protoplasm stained faintly reddish with the hematoxylin and eosin and Mallory trianiline stains.[13] Though too numerous to count, the altered

13. These cells have been termed "pregnancy cells" (*Schwangerschaftszellen*) by Erdheim and Stumme (Beitr. z. path. Anat. u. z. allg. Path. **46**:1, 1909).

chromophobe cells comprised at least 50 per cent of the cells of the anterior lobe. Some of these contained isotropic fat globules. Occasionally, round cell infiltrations were seen in the posterior lobe in the region of the lipoidgranuloma. The epithelial investment of the posterior lobe was particularly rich in basophils. In the intervening tissue between the anterior and posterior lobes termed by some "pars intermedia" were islands or groups of cells arranged around cavities filled with dense colloid material and lined with cuboidal epithelium (retention cysts resembling greatly the alveoli of the thyroid gland). Within the colloid substance were desquamated epithelial cells. In the posterolateral portion of the anterior lobe were several large cysts, which were lined with squamous, columnar, occasionally ciliated epithelium, and which contained a gelatinous substance (vestiges of the hypophyseal cavity).

Occasionally, plasma cells were seen. Isotropic droplets were seen throughout the epithelial elements of the anterior lobe, perhaps most marked in the basophils.

The posterior lobe consisted of dense, fairly acellular bands of matted together connective tissue fibers. The neuroglial elements were closely compressed; the interneuroglial spaces were practically obliterated. The entire lobe appeared atrophic and fibrotic, and there was a marked round cell infiltration.

Osseous System: Sections from the region of the cranial bone defect showed partial replacement of both tables by dense, acellular connective tissue which filled the diploe. The contiguous trabeculae showed arrested development. The osteoblasts were flat throughout. There was considerable evidence of bone destruction, namely, eroded trabeculae, in the vicinity of which were numerous osteoclasts. The dense connective tissue, which contained some blue-staining areas, probably calcified fibrous tissue, extended in places to the periosteum. Distal to the lesion there also appeared to be arrested development of the trabeculae.

Sections from the proximal portion of the right femur showed fibrous replacement of the spongiosa, so that the entire area involved resembled compact bone. The fibrous tissue extended between the trabeculae, often enclosing them entirely. In some areas there was considerable osteoblastic proliferation, the osteoid tissue being quite thick. In other areas osteoclastic changes predominated. A few of the haversian canals were dilated; the regional bone was eroded and contained lipoid cells. The predominant feature in the femur was the connective tissue replacement of the spongiosa by an osteosclerotic process.

Sections from the region of the sella turcica, ribs and vertebrae showed no significant changes.

Testes: These presented marked atrophy of the seminiferous tubules bilaterally, more marked on the left, with replacement fibrosis and hyalinization. The interstitial cells were greatly decreased in number. The remaining intact tubules showed complete loss of spermatogenesis.

Other Organs: The pineal body showed some hyalinization and connective tissue fibrosis with slight calcification.

The thyroid gland showed the follicles distended with colloid substances. The lining epithelium was flat. No lipoid cells were seen.

The pancreas showed slight autolysis. The islands of Langerhans were numerous, large and prominent. The nuclei of the epithelial cells were large and vesicular.

In the suprarenal glands, the medulla was unusually prominent and contained two definite ganglionic masses. The muscle coats of the suprarenal veins were irregularly hypertrophied. The cortex was thin. There was marked atrophy of the fascicular layer. The glomerular layer contained a moderate amount of lipoid substance.

The germinal centers of the lymph nodes were not distinct. There were several areas of hyalinization. The sinuses were filled with proliferated endothelial cells. No lipoid cells were seen.

In the spleen, the malpighian corpuscles were prominent. Small scattered areas of hemorrhage were present in the pulp. The sinuses were obscured; there was a slight increase in the endothelial elements. The walls of the smaller arterioles were thickened. There were no lipoid cells present.

The kidneys showed a moderate amount of parenchymatous degeneration. The glomeruli were normal.

In the prostate, some glands showed occasional epithelial hyperplasia. One gland was filled with proliferated epithelial cells.

The epididymis showed increased density of the connective tissue fibers between the tubules.

The gums showed cellular infiltration, consisting of plasma cells, lymphocytes and enlarged cells with vesicular nuclei. No lipoid cells were present.

The liver showed parenchymatous degeneration.

The tongue, esophagus, stomach, small and large intestines, gallbladder, diaphragm, heart, aorta, pulmonary artery, trachea, skin, and axillary and abdominal fat showed no significant abnormalities.

COMMENT

Age.—Hand's disease (Schüller-Christian syndrome) is seen most frequently in children, thirty-three of the fifty reported cases having occurred in children in the first decade of life. The youngest was 2 years old, and 50 per cent were less than 5 years old. Cases were reported as occurring in persons as late as the sixth decade, the oldest of these persons being 55 years.

No.		26	7	6	6	2	2	1
Age	0	5	10	20	30	40	50	60

Sex.—Males are predominantly affected in about the proportion of 2:1. Of fifty cases, thirty-four occurred in males and sixteen in females.

Etiology.—The etiology of this disease is unknown. In several instances lipemia with hypercholesteremia has been noted. Normal or even subnormal values of the fat and lipoid in the blood stream, however, are not incompatible with the existence of this disease. There is neither a climatic nor a geographic influence. Similar to other types of disturbances in lipoid metabolism (Niemann-Pick's disease and Gaucher's disease) it is particularly frequent among Jews. As the disease appears early in childhood, it is evident that occupation plays no important rôle. Frequently trauma appears to be the precipitating factor. According to the literature, heredity is not a factor, although there is one questionable instance of two cases occurring in one family (Herzenberg).

Symptomatology.—The sites of predilection for the deposition of the lipoid substances are the tissues of the head region, the structures being involved in the following order: (1) cranial bones, (2) orbit and (3) region of the pituitary gland and the tuber cinereum. The three cardinal symptoms of Hand's disease, (1) defects of the cranial bones, (2) exophthalmos and (3) diabetes insipidus, are directly referable to the lipoidgranulomatous deposits in these regions.

1. The skeletal system is particularly prone to lipoidgranulomatous involvement. The predominant osteoclastic changes in the cranial bones give rise to the palpable, often pulsating and roentgenologically demonstrable, cranial bone defects. The roentgenogram of the skull is characteristic, giving rise to the *landkarten Schädel* ("map skull") (Schüller). The process is not merely confined to the cranial bones, but may also involve other parts of the skeleton, namely, the humeri, femurs, scapulae, ribs, vertebrae and pelvic bones (Thompson, Keegan and Dunn; Hochstetter and Veit; Schultz, Wermbter and Puhl; Rowland; Herzenberg, Schüller and Chiari; Sosman; Ighenti, and others). In the case reported in this communication, the sacrum, femur and tibia were also involved. There was also cloudiness of the left antrum of Highmore with irregularity of the medial wall due to bony involvement. Thompson, Keegan and Dunn and Herzenberg also reported sinus involvement. The severe skeletal pains are subsequent to the lipoidgranulomatous changes and are particularly marked when the lesions are near the periosteum.

2. The exophthalmos, which is sometimes unilateral (Hand, case 3; Schüller and Chiari) and exceptionally absent (Globig; Herzenberg; Sosman; our case), is due to the destruction of the orbital plate of the frontal bone by the granulomatous process, which at times may involve the retro-orbital structures (Rowland, case 1; Schüller and Chiari; Wheeler). Lipoidgranulomatous involvement of the sympathetic fibers to the müllerian muscle may also be a factor in the causation of the proptosis.

3. The diabetes insipidus syndrome is referable to lipoidgranulomatous involvement of either the pituitary gland or the region of the tuber cinereum. Occasionally, as in our case, both of these structures show extensive involvement. Roentgenograms of the region of the sella turcica may show extensive destruction of the floor of the sella turcica and clinoid processes (Christian; Rowland, case 2; Cohen, Moreau and Murdoch; Pickham and Joel). On the other hand, this may be perfectly normal (Grosh and Steffel; Hand, case 2; Hausmann and Bromberg; our case, and others).

Besides the cardinal symptoms forming the diagnostic triad of defects in the cranial bones, exophthalmos and diabetes insipidus, there are inconstant, though very significant other clinical findings in Hand's disease, as follows:

1. Gingivitis occurs with painful gums and falling out of the teeth due to lipoidgranulomatous destruction of the alveolar processes of the maxillary bones, though this may be influenced as well by the lesion in the pituitary gland. These symptoms are frequently present very early in the disease, and it is not uncommon for the dentist to note the presence of a peculiar yellowish granulation tissue in the socket of an extracted tooth or about the gum of a loose tooth.

2. Endocrine dyscrasias are found. Of these, the most common is dystrophia adiposogenitalis (Fröhlich's syndrome) as in the instances reported by Schüller, Kyrklund, and Schüller and Chiari. Dwarfism was noted by Grosh and Steffel, Alberti, Schultz, Wermbter and Puhl, and Rowland. Simond's cachexia was reported by Hochstetter and Veit in a case with a pluriglandular syndrome. The asthenia is often unusually marked. Mental and physical retardation are mentioned by many authors. Our case showed a pluriglandular picture with predominant features of dyspituitarism.

3. Splenohepatomegaly was noted by Herzenberg, Schultz, Wermbter and Puhl, and Ighenti. Wiedman and Freeman noted icterus associated with hepatomegaly due to obstruction of the portal passages by involved glands.

4. Lymphadenopathy was noted by Berkheiser, Vampré, Herzenberg, Ighenti, and Kartagener and Fischer.[14] The barely palpable axillary lymph nodes in our case showed lipoid cells on biopsy.

5. The neurologic manifestations of this disease are varied, depending on the localization of the granulomatous lesions. Thus signs of increased intracranial pressure are mentioned by Hochstetter and Veit, Schüller and Chiari, and Frumann-Dahl and Forsberg. In the case of Schüller and Chiari, focalizing signs of intracranial tumor were present as well. Signs referable to diffuse involvement of the central nervous system were present in our case. This aspect will be reported in a subsequent publication from the Neuropathological Department by Dr. Charles Davison.

6. Cutaneous lesions were noted by Hand, Herzenberg, Höfer and Ighenti. These may vary from bronzing to maculopustular, hemorrhagic or seborrhea-like lesions. Lipoid infiltrations of the eyelids (*Dachshund-Augen*) have been reported by Schüller and Chiari, Hochstetter and Veit, Pussey and Johnstone, and Kartagener and Fischer.

7. Transient impotence was present in our case as well as in the instance reported by Hochstetter and Veit.

8. Disturbances in hearing are mentioned by Höfer. Ighenti's patient had an external otitis. Turner, Davidson and White reported involvement of the mucous membrane of the mouth, larynx, trachea and bronchi. In this case, trachectomy was performed because of laryngeal obstruction by a lipoid granulomatous mass.

9. Cor pulmonale with failure of the right side of the heart was reported by Thompson, Keegan and Dunn. Chester reported cor pulmonade due to collapse induration of the lungs subsequent to lipoidgranulomatous infiltrations in a type of lipoidgranulomatosis confined to the skeletal system (not in the cranial bones) and the internal organs.

10. Susceptibility to infection at the site of the local lesion as well as to intercurrent often terminating infections is a characteristic feature. In our case, the formation of persistent draining sinuses at the areas operated on is noteworthy.

Because of the widespread lesions and the subsequent protean clinical manifestations, a differential diagnosis offers considerable difficulty. A review of our case alone illustrates this contention. The diagnoses considered were the following: (1) various types of neoplasm with skeletal metastases, such as Ewing's sarcoma, sarcoma of the reticulo-

14. Kartagener, M., and Fischer, H.: Ztschr. f. klin. Med. **119**:421, 1932.

endothelial system, primary pituitary neoplasms, multiple myeloma; (2) Hodgkin's disease; (3) various types of granulomas, such as syphilis, tuberculosis, actinomycosis, glanders; (4) chronic nonspecific granuloma.

Apart from the presented classic picture of Hand's disease and the unusually extensive involvement of the central nervous system, this case is particularly interesting because of its endocrinologic aspects. The patient presents the clinical picture of dyspituitarism, namely, marked skeletal overgrowth, long arms, thick wrists, big feet, adiposity, wide pelvis, female distribution of pelvic hair, gluteal pads of fat, coarse, pseudomyxomatous, waxlike color of the skin, hypotrichosis of the face and lower extremities, asthenia, drowsiness, bradycardia, low blood pressure, subnormal temperature, lack of perspiration plus diabetes insipidus and loss of libido. The enlargement of the anterior lobe of the pituitary gland associated with a marked diminution of the number of eosinophils, a definite hyperplasia and hypertrophy of basophils, an increase in the stroma, presence of a lipoidgranuloma in the capsule, a peculiar transformation of the chromophobe cells and marked fibrosis, atrophy and round cell infiltration of the posterior lobe is striking. The hyperplasia and hypertrophy of the basophils are noteworthy. It is of interest to note that Cushing, at a recent meeting of the Section of Neurology of the New York Academy of Medicine, suggested the possibility of an unusual clinical syndrome associated with basophilic adenoma of the pituitary gland. Kraus [15] attempted to draw a relationship between constitution and the basophilic content of the anterior lobe of the pituitary gland. Designating a patient of normal proportions as mesothenic, he denoted the basophilic content of the anterior lobe as 3 plus. Asthenic persons, as those with tuberculosis or Addison's disease, have a greatly diminished number of basophils, while hyperasthenic and obese patients have a greatly increased basophilic content. Thus the habitus in this case may be a factor related to the unusual number of basophils. The pituitary struma by pressure on the optic chiasma was possibly responsible for the marked diminution of vision and temporal notching of the visual field, both of which had increased in degree at the second admission to the hospital. Reuse [16] noted transient bitemporal hemianopia during pregnancy, which disappeared after parturition.

There is a definite reciprocal relationship between the pituitary gland and the testes. The association of lesions of the pituitary gland with subsequent gonadal atrophy has been noted by Custriny,[17] Bar-

15. Kraus, E. J.: Virchows Arch. f. path. Anat. **268**:315, 1928.

16. Reuse, cited by Erdheim, J., and Stumme, E.: Beitr. z. path. Anat. u. z. allg. Path. **46**:1, 1909.

17. Cited by Kon, J.: Beitr. z. path. Anat. u. z. allg. Path. **44**:233, 1908.

tels,[18] Cushing [19] and Biedel.[18] It is of interest to note, however, that Tandler and Gross [20] reported roentgen changes in the sella turcica in eunuchs. In the instance reported in the present communication, we believe that the changes in the pituitary gland are primary and testicular atrophy secondary for the following reasons:

1. In women following roentgen castration, Kon,[21] Kolde [22] and Rössle [22] found engorgement of the pituitary gland. In these instances, marked hyperplasia and hypertrophy of the eosinophils and striking diminution of the basophils were noted. In a case of absence of the ovaries, Olivet [22] reported a large pituitary gland showing a marked increase in the eosinophils and a small nodule of main cells.

In eunuchs, the increase in the weight of the pituitary gland as shown by Fischerer [17] is due to a marked increase in the eosinophils. Only in rare instances, notably the cases of Garfunkel [23] and Kon,[21] were the findings different. In these there was a diminution in the eosinophils and basophils, and the chromophobe cells showed the changes associated with pregnancy, namely, the appearance of "pregnancy cells."

2. In cases of dyspituitarism of the Frölich type, the testes may show no abnormality.

3. The early symptoms of dyspituitarism in this case, as already noted, were present years before the impairment of libido or of potency.

In view of the gonadal atrophy it is significant to note the prominence of the islands of Langerhans in the pancreas. Gottlieb [22] and Rössle [22] reported hypertrophy of these islands after loss of testicular function.

In the differential diagnosis the frequent confusion with multiple myeloma is striking. In Gilmore's case of Hand's disease,[24] Bence-Jones protein was found in the urine, making the diagnosis even more difficult. In view of the skeletal changes and the fact that the Bence-Jones albuminose is present in other conditions even when there is no skeletal involvement, Bence-Jones albuminose should be looked for in every case of Hand's disease. Tumors with skeletal metastases as carcinomas of the prostate, thyroid gland, bronchus, breast, etc., as well as hypernephroma, should also be excluded.

The "peculiar yellow" sputum in this disease, provided it is not due to fatty degeneration of a pneumonic process, may be of value in detecting pulmonary involvement in the absence of roentgen findings.

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18. Cited by Garfunkel, B.: Beitr. z. path. Anat. u. z. allg. Path. **72**:475, 1924.

19. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

20. Tandler and Gross: Wien. klin. Wchnschr. **21**:277, 1908.

21. Kon, J.: Beitr. z. path. Anat. u. z. allg. Path. **44**:233, 1908.

22. Cited by Kraus, E. J.: Drüsen mit innerer Sekretion, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

23. Garfunkel, B.: Beitr. z. path. Anat. u. z. allg. Path. **72**:475, 1924.

24. Gilmore, M. E.: Texas State J. Med. **21**:358, 1925.

The relief from some of the subjective symptoms at the time the patient was receiving roentgen therapy is significant. Schüller first noted the symptomatic and roentgenologic improvement in the skeletal lesions with roentgen therapy. It is very likely that the irradiation accelerates the healing process, which of itself goes on to fibrosis. Spontaneous remissions, however, occur, and progressive lesions may be detected during the course of roentgen therapy (our case and numerous others). A diet in which fat is low and various endocrine products (thyroid, parathyroid, pituitary, insulin) have been tried without success.

The evidence is insufficient for an attempted correlation of the unusual changes in the pituitary gland with this generalized disturbance of lipoid metabolism. It is apparent that the changes in the pituitary gland are not subsequent to roentgen therapy.

SUMMARY [25]

A case of lipoidgranulomatosis (type, Hand-Schüller-Christian) in a man of 31 years with diffuse skeletal involvement, diabetes insipidus, dyspituitarism and extensive changes in the central nervous system is described.

Postmortem examination showed (*a*) lipoidgranulomatous lesions in the skull, femur, pituitary gland and lungs and (*b*) increased vascularity in the anterior lobe of the pituitary gland, marked diminution in the number of the eosinophilic cells, adenomatous hyperplasia and hypertrophy of the basophilic cells, a predominance of altered chromophobe cells and an increase in the stroma. The posterior lobe showed an increase in the stroma, marked fibrosis and round cell infiltration.

The atrophy of the testicles, with its attendant clinical picture, was subsequent to a primary lesion of the pituitary gland.

25. For the sake of brevity we have listed in the footnotes only the most comprehensive bibliographic articles. Detailed references to all the cases mentioned may be found in the publications cited in footnotes 1 to 9 and 14 and 24. A complete review of the literature may be found in the publications cited in footnotes 4 to 10.

MECHANISM OF CALCIFICATION IN THE HEART AND AORTA IN HYPERVITAMINOSIS D

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Many confusing elements may be found in the explanations that pertain to the action of vitamin D, particularly with regard to the toxic effect which may be observed when experimental animals are given enormous doses of irradiated ergosterol. First, there has been some controversy as to whether the toxic effects were the result of the action of the vitamin or of that of other substances in the preparations used, but recent work, particularly that of Harris and Moore,[1] and that of Harris and Innes,[2] appears to demonstrate that, in sufficiently large doses, the vitamin per se is toxic. Second, there is the problem whether the vitamin may not have a dual action, its beneficial effects in the treatment of rickets representing a different sort of activity from that observed in toxic hypervitaminosis. Third, there is the problem of whether, both in therapeutic and toxic doses, it has a local action on tissue or whether its action is only a general one on the calcium metabolism. Fourth, there is still a difference of opinion concerning its manner of action, some thinking it increases the solubility of calcium in the blood, and others that it acts through the agency of the parathyroid gland or of its hormone.

It would seem that a solution of the problem concerning the mechanism of calcification in hypervitaminosis D would be of no small assistance in understanding some phases of the action of the vitamin. Many investigators have reported on the appearance of changes in the recipient tissues which are preliminary to the calcifications, and Vanderveer [3] in a recent article depicted the results of careful histologic study in this field. Most of the experiments of this nature, however, have been conducted by the administration of the ergosterol over a relatively long period of time, so that there are difficulties in the way of deciding on the early changes. In this respect, the method used by Laas [4] has much to commend it, as he administered the substance in single massive doses, and found that there was a latent period of only four days before calcifica-

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1. Harris, L. J., and Moore, T.: Biochem. J. **22**:1461, 1928; **23**:261, 1929.
2. Harris, L. J., and Innes, J. R. M.: Biochem. J. **25**:367, 1931.
3. Vanderveer, H. L.: Arch. Path. **12**:941, 1931.
4. Laas, E.: Virchows Arch. f. path. Anat. **278**:346, 1930.

tions occurred. In any event, there is at this time a considerable amount of opinion that leans to the point of view that in hypervitaminosis D there are evidences of degeneration in the tissues before calcifications occur.

A decision as to the sequence of events in the tissues demonstrating calcification is of utmost importance, because it would throw a great deal of light on the question whether the action of the toxic doses is a local injurious one on tissues or only a general one on the calcium metabolism. In other words, it is important to decide whether the calcifications are the result of degenerative changes in the tissues or of a precipitation of calcium from the blood. In this connection, pathologic calcifications may be divided into two broad groups. The first group depends for causation on the degenerative changes in the recipient tissues, and the mechanism may be either that described by Klotz,[5] which depends on the breaking-down of fat with the formation of soaps and later more permanent deposits of calcium, or that of Wells,[6] which depends on the tissues assuming characteristics more physical than chemical, which enable them to bind calcium. The second group of pathologic calcifications, are, however, fundamentally different, so far as their etiology is concerned. They depend for their causation, not on degenerative changes in the recipient tissues, but on a change in the blood, so that it becomes unable to retain all its calcium in solution. A good example of calcifications that depend on this second type of mechanism may be found in the metastatic calcifications seen in hypercalcemias associated with certain parathyroid tumors.

This work is, therefore, concerned with a study of the sequence of events in the tissues in order that the calcifications may be classified. It was thought advisable to produce the lesions not only by long continued administration of vitamin D but also by administration of massive single doses, so that the cycle of events could be clearly followed. In one series, animals were killed each twenty-four hours after a large single dose of activated ergosterol.[7] One other point regarding the experimental procedure is of interest, namely, the method by which calcium was demonstrated in the tissues. Since it is evident from the work of Cameron [8] that neither hematoxylin nor silver preparations are specific

5. Klotz, O.: J. Exper. Med. **7**:633, 1905; **8**:322 and 504, 1906.

6. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

7. In this paper the term "activated ergosterol" refers to irradiated ergosterol of unusual potency. The term "viosterol" is used in this paper as the substance commonly employed in therapeutic procedure. Strictly speaking, viosterol is a designation for irradiated ergosterol, but in the sense used in this paper it applies only to the strengths as found in the commerical preparations.

8. Cameron, J. R.: J. Path. & Bact. **33**:929, 1930.

stains for calcium, it was thought that the technic of incineration, as used by Policard,[9] Policard and Okkels [10] and Scott [11] for the detection of mineral content in microscopic sections, might prove to be the best method for demonstrating any increase in mineral content in the tissues. Duplicate sections of the stained preparations were prepared throughout the work by this technic.

MATERIAL AND METHODS

Forty rats of good laboratory stock were used in the experiments. These were divided into four series.

Series 1 consisted of seven experimental animals and seven controls. The animals were full-grown males. Each received approximately 3 cc. of viosterol, 250 D, per day. One experimental animal and one control were killed each fifth day.

Series 2 consisted of five rats, each of which was given 3 cc. of viosterol, 250 D, each day. They were killed at various times ranging from twenty-eight to thirty-eight days.

Series 3 consisted of seven experimental and four control young animals. Each of the former received 0.33 cc. of activated ergosterol 10,000 X, at the beginning of the experiment. One rat was killed at the end of forty-eight hours, and on the fifth morning the remaining six rats were found dead in the cage.

Series 4 consisted of ten half-grown male rats. Each of these received 0.25 cc. of activated ergosterol 10,000 X at the beginning of the experiment, and two rats were killed each twenty-four hours following the single administration.

The vitamin was administered per os by a dropper in series 1, and by mixing it with the food in the other three series. The animals were on a stock laboratory diet which contained an ample supply of calcium. The animals were in every case killed by ether anesthesia. Three animals in series two were given an injection of alizarin red, 2 cc. of a 1 per cent solution. Material taken at autopsy included the heart, aorta, lungs, spleen, liver, kidneys, thyroid and parathyroid glands, long bones and incisor teeth. Specimens were fixed in formaldehyde, Flemming's solution and alcohol formaldehyde. Some frozen sections were cut and stained for fat with scarlet red. Paraffin sections of the complete series were stained with hematoxylin and eosin. Other sections were stained with alizarin and with osmic acid and safranin. A complete set of serial sections duplicating the hematoxylin and eosin series was prepared for incineration by the following technic: The fixative used was 9 parts absolute alcohol and 1 part neutral formaldehyde. Blocks were then moved directly into absolute alcohol and embedded by the usual method in paraffin. Sections were then cut and floated on slides with paraffin oil. Sections were then incinerated for ten minutes at approximately 178 C., five minutes at approximately 256 C., five minutes at approximately 350 C., five minutes at approximately 454 C., five minutes at approximately 556 C., and a minute and a half at approximately 600 C. They were examined by dark field illumination.

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9. Policard, A.: Protoplasma **7**:464, 1929.
10. Policard, A., and Okkels, H.: Anat. Rec. **44**:349, 1930.
11. Scott, G. H.: Bull. d'histol. appliq. à la physiol. **7**:251, 1930.

OBSERVATIONS

In series 1, each experimental animal received daily 3 cc. of viosterol and an animal was killed about every fifth day. The aortas showed little change until the seventh rat was killed, after thirty-nine days of the administration of viosterol. This rat showed a definite calcareous deposit in the outer third of the aortic media, which appeared in the hematoxylin and eosin sections to be in the forms of an incrustation on the elastic fibers and a diffuse calcification of several of the muscle cells situated between the elastic fibers. The coronary vessels appeared to be normal.

Series 2 consisted of five animals which received viosterol for from twenty-eight to thirty-eight days. It was administered by mixing it with their food. The aortas of three of these animals showed calcareous deposits. These were found in greatest numbers in the arch and fairly frequently in the upper part of the descending aorta. The animals given an injection of alizarin red showed clearly, in the gross, pinkish areas in the wall of the vessel. On section, a rather patchy distribution of the lesions was found, areas of calcareous deposit being scattered in the inner, middle and outer thirds of the media. When the lesion was extensive, it was usually located in the inner third of the media. In the hematoxylin and eosin preparations, the lesions showed as incrustations along the elastic fibers together with scattered calcifications of the area normally occupied by muscle cells and fibroblasts between the elastic fibers. At the site of a lesion, the elastic fibers were often spread widely apart, sometimes to two and three times the normal distance. In the animals showing calcification of the aorta, the cardiac musculature showed patchy areas of calcification, which were often associated with necrosis of tissue and infiltration by mononuclear and polymorphonuclear leukocytes. The branches of the coronary vessels afforded perhaps the best illustration of the calcareous lesion seen in the animals. In the sections stained with hematoxylin and eosin, these vessels stood out strikingly as edematous, amorphous, granular, blue-colored rings, when cut in cross-section, in which nuclei and cell outlines could be identified only infrequently. The muscle cells of the media appeared to be affected to the greatest extent, and the region about the coronary vessels often showed marked inflammatory cell infiltration associated with calcium deposits. The incinerated sections showed the coronary vessels standing out as bright rings containing greatly increased amounts of mineral matter. The plaques in the aorta were also seen to contain large amounts of mineral matter. The elastic fibers, which showed little mineral matter in normal sections, were also seen to become involved in the process and on occasion appeared to be heavily infiltrated with mineral.

The sections fixed in Flemming's solution and stained with osmic acid showed only a slight amount of fat in the calcareous lesions, nothing of any note. Frozen sections stained with scarlet red showed the same results.

Thus the lesions encountered in this series of animals showed edematous areas in the aortic wall containing large amounts of mineral, probably calcium, which was evident in the degenerating and necrotic muscle tissue, but which was most marked at the periphery of these lesions, where it formed incrustations on the adjacent elastic fibers. In many instances, the latter appeared to be completely calcified as well, demonstrating fractures and other evidences of degeneration and necrosis. The coronary vessels were most markedly calcified, the muscular media being the chief site of involvement. Furthermore, patchy areas of the cardiac musculature were also calcified, and both these areas and the coronary vessels

showed inflammatory cells present about them. The greater calcification in this series over the first series may be ascribed to the method by which the viosterol was administered.

In series 3, each experimental animal received one single dose of activated ergosterol 10,000 X. The first animal was killed forty-eight hours after receiving a single dose; it showed extensive calcifications of the coronary vessels together with patchy areas of calcification in the cardiac muscle and aorta. The remaining six animals of this series died at approximately the end of ninety-six hours; they also showed extensive pathologic lesions. The most striking feature of the picture was found in the coronary vessels, which showed their media to be converted to amorphous-like material, which in the hematoxylin and eosin preparations appeared to contain a large amount of calcium, a finding that was substantiated by the incinerated sections, as they showed greatly increased mineral content. Again there was an inflammatory cell infiltration about the coronary vessels as well as

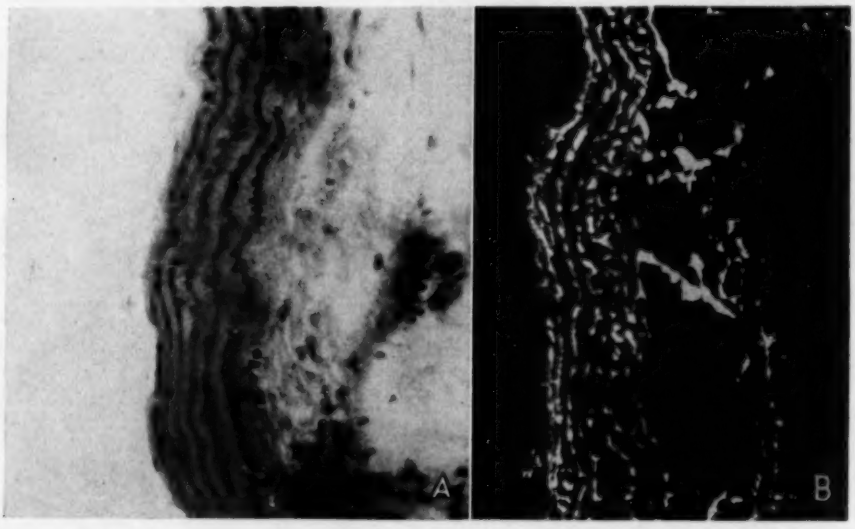

Fig. 1.—*A*, section of normal rat aorta; hematoxylin and eosin stain; × 250. *B*, incinerated section of normal aorta; dark field illumination; × 250. The elastic fibers may be seen as clear bands between the muscle cells and fibroblasts.

some patchy inflammatory areas in the cardiac musculature not intimately related histologically to vessels but demonstrating calcification.

Because of the relatively swift production of the lesion, it was thought advisable to duplicate the procedure used in series 3 with a slightly smaller dose and kill animals each twenty-four hours in order to find the preexisting picture corresponding to the characteristic one found in series 3. Consequently, in series 4, ten animals were utilized, and two were examined each twenty-four hours. Photomicrographs of this series are to be seen in figures 2 and 3.

At twenty-four hours, in series 4, the hematoxylin and eosin sections showed no obvious change from the normal (fig. 1). Incinerated sections showed the muscle fibers and coronary vessels to possess approximately the same mineral content as the normal ones. The aorta showed a regular distribution of elastic tissue with no obvious increase in mineral in the muscle cells of the media (fig. 2 *A* and *B*).

At forty-eight hours, lesions were prominent. In the stained sections, the coronary vessels showed marked thickening caused by an edematous amorphous change of the musculature of the vessels, which took a deep blue stain with the hematoxylin. Patches of musculature, usually but not always related to vessels, also showed this change in the cytoplasm of the cells, and these areas as well as the vessels showed an inflammatory cell infiltration about them. Sections from

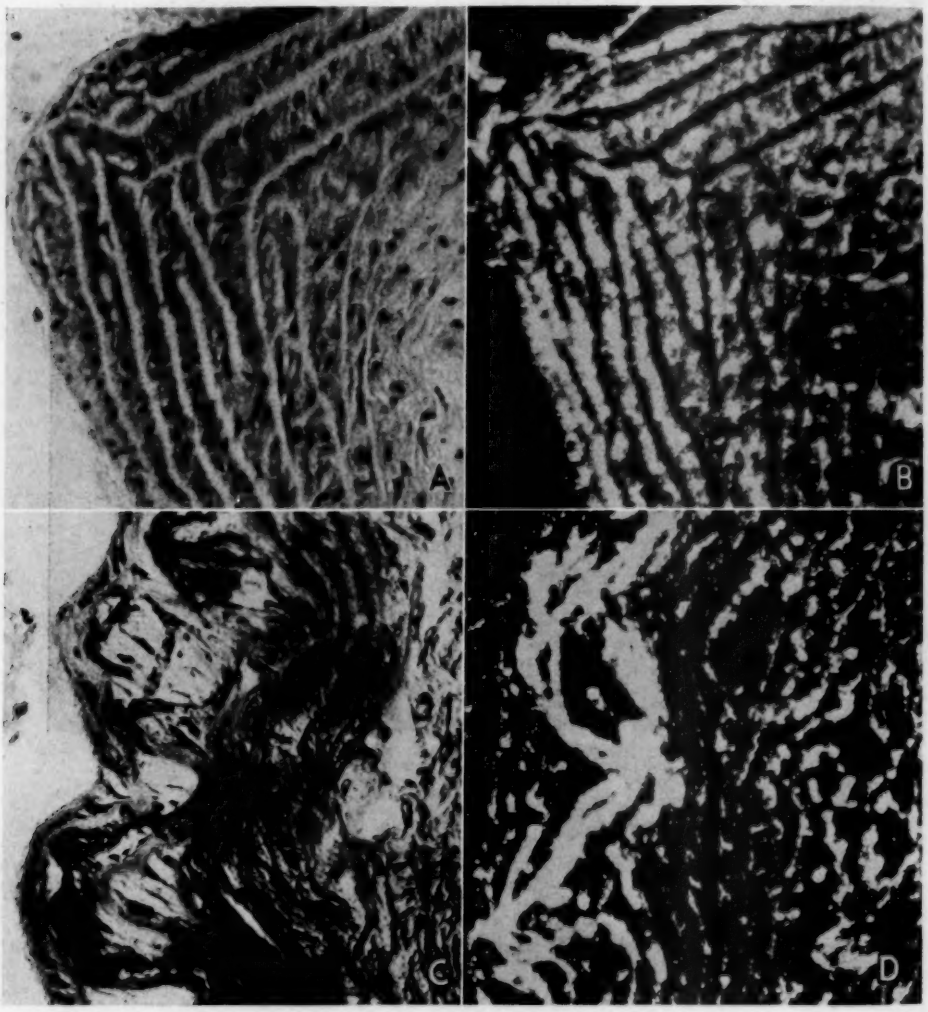

Fig. 2.—*A*, section of rat aorta twenty-four hours after administration of activated ergosterol; series 4; hematoxylin and eosin stain; × 250. No obvious degeneration is evident. *B*, incinerated section from same block as *A*; dark field illumination; × 250. The elastic fibers are still seen as clear bands. *C*, section of aorta forty-eight hours after administration of activated ergosterol; series 4; hematoxylin and eosin stain; × 250. The characteristic lesion may be noted. *D*, incinerated section from same specimen as *C*; dark field illumination; × 250. Note the great increase in mineral content in lesion.

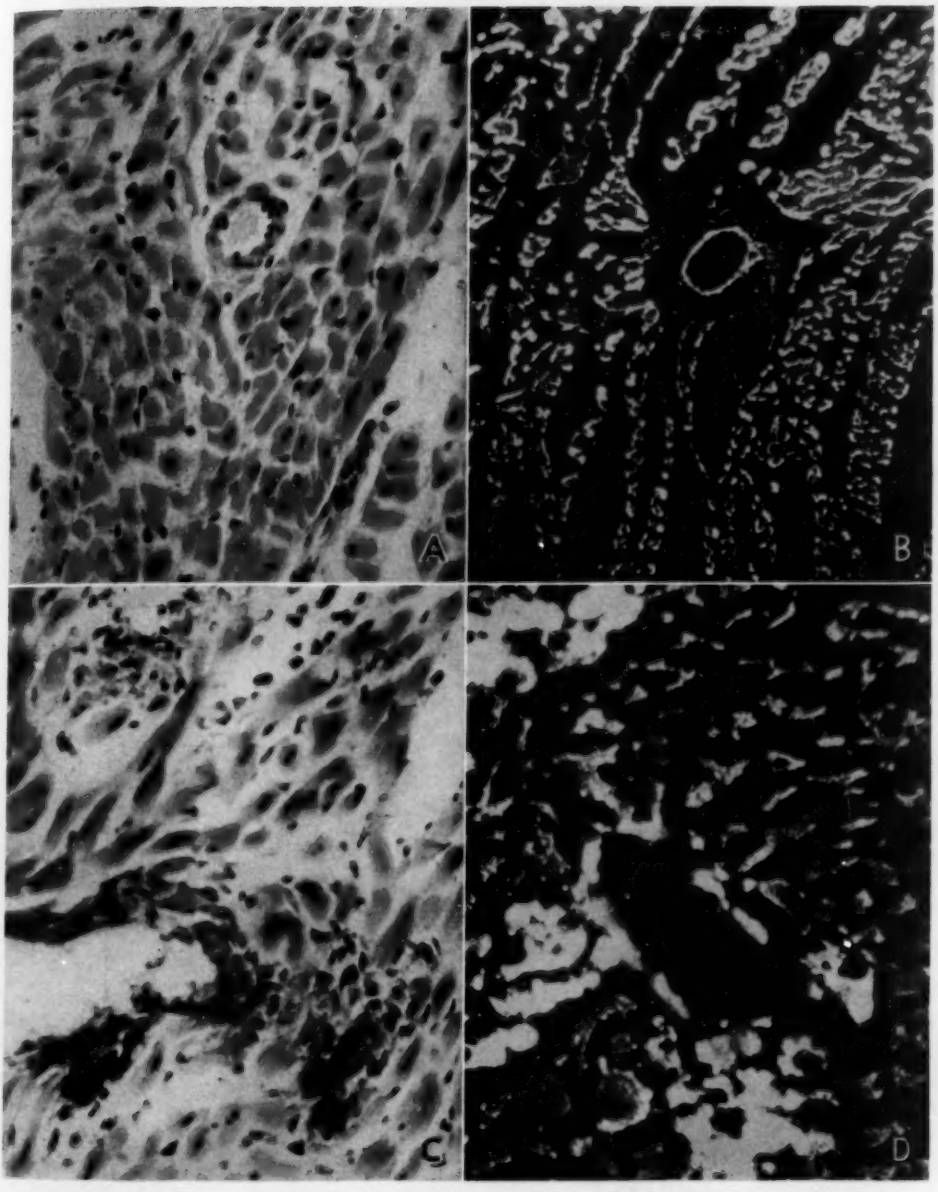

Fig. 3.—*A*, section of cardiac muscle and coronary vessel twenty-four hours after administration of activated ergosterol; hematoxylin and eosin stain; × 250. No evidence of calcification or of marked degeneration is present. *B*, incinerated section from same specimen as *A*; dark field illumination; × 250. Note the normal distribution of mineral. *C*, section of cardiac muscle and coronary vessel forty-eight hours after administration of activated ergosterol; hematoxylin and eosin stain; × 250. The calcification of the vessel and part of the cardiac muscle may be seen together with the inflammatory cell infiltration. *D*, incinerated section of same preparation; dark field illumination; × 250. Note the great increase in mineral matter in the wall of the vessel and in certain areas of cardiac muscle.

the arch of the aorta showed edematous areas in the inner third of the media, which were situated between adjacent elastic fibers. These showed areas of deep blue staining, which was deepest along the elastic fibers (figs. 2 *C* and 3 *C*).

The incinerated sections showed a striking series of pictures. The coronary vessels in the heart stood out as thick-walled tubes of mineral matter (fig. 3 *C* and *D*). The change from the picture twenty-four hours earlier was remarkable.

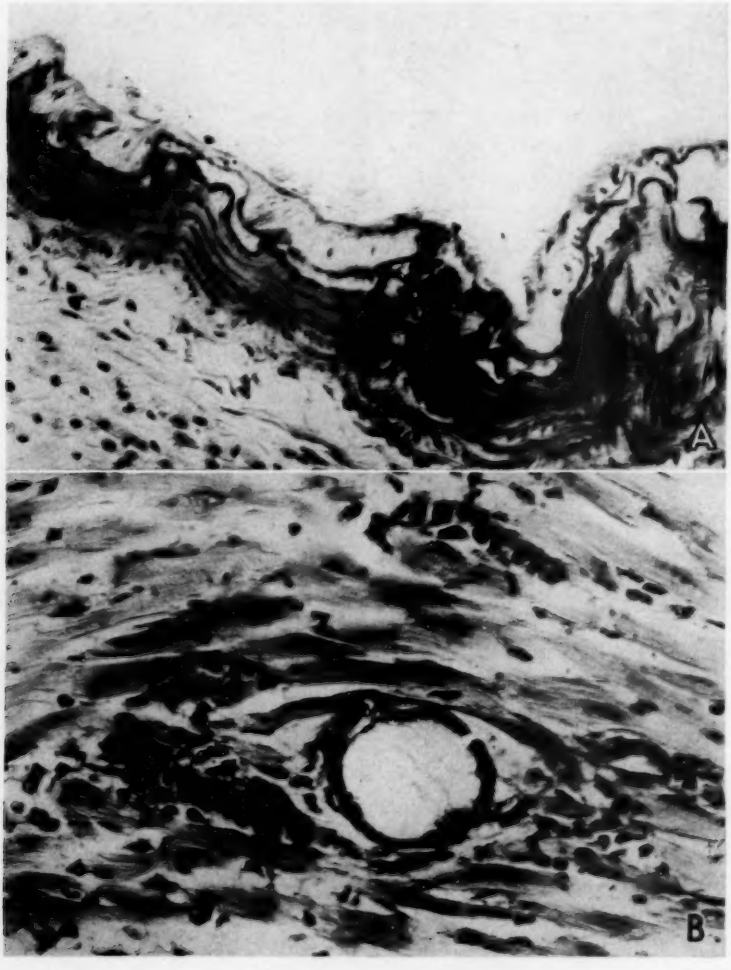

Fig. 4.—*A*, typical lesion produced in aorta by a single enormous dose of activated ergosterol; hematoxylin and eosin stain; × 200. *B*, typical picture of calcified coronary vessel, calcified cardiac muscle and inflammatory cell infiltration produced by one single enormous dose of irradiated ergosterol; hematoxylin and eosin stain; × 300.

The cardiac musculature also revealed the patches observed in the hematoxylin and eosin sections to be heavily infiltrated with mineral (fig. 3 *C* and *D*). The aorta showed the edematous patches in the inner third of the media to be also heavily infiltrated with mineral matter (fig. 2 *C* and *D*).

At seventy-two hours, much the same type of picture was shown as that observed at forty-eight hours. Each section of the heart showed the same type of inflammatory cell infiltration about the coronary vessels, and the latter as well as the aorta showed relatively huge amounts of mineral deposit.

Before attempting to discuss the significance of the results obtained in this work, the method by which calcium was demonstrated should be commented on. It is apparent that there was, in the sections, a fairly close correlation between the deposits stained by hematoxylin and the deposits shown by the incineration technic to be mineral matter. Furthermore, these same plaques in animals given an injection of alizarin red were colored, so that there seems to be good reason to believe that hematoxylin demonstrates fairly well rather massive deposits of calcareous material when these are formed in the body.

On the other hand, there is good reason to suspect that the incinerated pictures rather minimize the increase of calcium which occurs in the pathologic lesions. The normal incinerated section demonstrates all the mineral ash, only a part of which is calcium, but it is probable that the increase in mineral content at the site of the lesions is almost all calcium, so that the increase in calcium is probably much greater than is apparent.

COMMENT

It has been stated previously that an important problem concerns the calcifications of hypervitaminosis D, whether they belong to the group dependent on degenerative changes in the recipient tissues or to the group dependent on the inability of the serum to retain all its calcium even in the vicinity of normal tissues. Calcifications of this second type are not uncommonly seen in certain examples of hyperparathyroidism. They have been produced experimentally with excessive doses of parathyroid hormone by both Leaner [12] and Hueper.[13] Katase [14] described calcifications of this sort which were produced by injecting calcium salts into the body by several different routes. Furthermore, Rabl [15] and later Butler [16] produced calcifications in mice on a high calcium intake by alternating acid and basic diets.

On turning to the experiments performed in this particular work, it is evident that the striking feature was the extreme rapidity with which calcifications of the aorta, coronary vessels and cardiac musculature could be produced. Only second in importance is the fact that twenty-four hours after the administration of the activated ergosterol and only

12. Leaner, A.: J. Lab. & Clin. Med. **14**:921, 1929.
13. Hueper, W.: Arch. Path. **3**:14, 1927.
14. Katase: Beitr. z. path. Anat. u. z. allg. Path. **57**:516, 1914.
15. Rabl: Virchows Arch. f. path. Anat. **245**:542, 1923.
16. Butler, M.: Proc. New York Path. Soc. **24**:79, 1924.

twenty-four hours before the appearance of massive calcifications, there were no marked degenerative lesions in the described tissues which would presage such an imminent catastrophe. Furthermore, the massiveness of the calcification together with the previous points commented on would indicate almost beyond question that the calcifications of hypervitaminosis D produced by this experimental procedure belong to the type of calcification that is dependent on the inability of the serum to retain all its calcium, rather than on preliminary degenerative changes in the recipient tissues.

This conclusion seems to be the only one that would be in harmony with other recent observations regarding the toxic action of the vitamin. Bills and Wirick [17] showed that the toxicity of irradiated ergosterol could be intensified by increasing the amounts of calcium in the food. More recently Harris and Innes [2] performed some exceedingly interesting work in this direction and may be quoted as follows:

> An increase in the calcium content of a diet intensifies the severity of the hypervitaminosis and gives rise to an increased formation of the calcareous deposits, at a given level of vitamin D excess. With diets virtually devoid of calcium and phosphorus, on the other hand, a hypervitaminosis of a distinctive character can still be produced provided now that the level of vitamin D excess is sufficiently raised; under these conditions calcareous deposits are not in evidence but there is a greatly increased resorption of bone substance.

These findings appear to indicate that the calcifications seen in hypervitaminosis depend, not on the direct action of the vitamin on the tissue, but on its ability to so disturb the calcium metabolism that calcifications are produced. Therefore in contrast to the sequence of events usually observed in the calcifications that occur under a normal calcium metabolism, it appears that in hypervitaminosis D the degenerations observed in the lesions are a result of the disturbance of calcium metabolism, if not of the deposition of calcium.

In considering the manner in which calcifications of normal tissue may be produced by means of alterations of the calcium metabolism, a rather complicated problem is encountered. The calcifications do not appear to depend on simple hypercalcemia. It should be remembered that normally the blood contains more calcium than can be explained by the laws of simple solution. Furthermore one must visualize a mechanism by which the blood is able to build up a high calcium content and yet be unable to retain it in solution. Many of the data regarding the manner in which calcium is carried in the blood have been reviewed and discussed in previous contributions (Ham [18]) as well as the hypothesis which relates to the equilibrium that exists between the

17. Bills, C. W., and Wirick, A. M.: J. Biol. Chem. **86**:117, 1930.

18. Ham, A. W.: Cartilage and Bone, in Cowdry: Special Cytology, ed. 2, New York, Paul B. Hoeber, Inc., 1932; Angle Orthodontist, to be published.

nondiffusible calcium of the blood, the diffusible calcium of the blood and the calcium of the bones. The uncertainties that exist regarding some phases of the calcium metabolism render an understanding of the mechanism of precipitation rather difficult, but there seems to be sufficient evidence to describe at least three possible mechanisms by which the blood could acquire more calcium than it could retain at a later time. These will now be briefly considered.

1. Wells [6] described a mechanism which could account for the precipitation of calcium in the tissues in cases of hypercalcemia by considering that saturated serum of high carbon dioxide content would be forced to release calcium if the reaction of the serum became more alkaline. This mechanism would account for the deposition of calcium in the lungs, if serum saturated with calcium passed through the lungs and lost carbon dioxide, and this explanation has been used to account for the calcifications which appear to occur in cases of hypercalcemia in other areas of acid excretion. It should be remembered, however, that the serum normally contains more calcium than can be accounted for by the laws of simple solution, and as it is very probable that the serum calcium exists in both a nondiffusible and a diffusible form, it is also probable that this explanation instead of applying to the total serum calcium concerns more particularly the diffusible form.

2. A second factor which also comes into play regarding the solubility of the calcium of the blood is well illustrated by findings that have been recorded in certain cases of hyperparathyroidism by Bulger, Dixon, Barr and Schregardus.[19] They pointed out the tendency for a reciprocal rise and fall of the calcium and phosphorus levels, and showed that the blood calcium level could be lowered by the administration of sodium *ortho*-phosphate. If one applies the theory concerning the solubility product of electrolytes in solution, it is apparent that when the ionized calcium of the blood is near the saturation point, the addition of further ions to the serum could easily result in the precipitation of the less soluble calcium salts. These authors suggested this possibility, and the recent work of Hess, Benjamin and Gross,[20] who administered sodium bicarbonate in experimental hypercalcemia, and found that this procedure not only lowered the blood calcium level but caused an increase in the amount of calcium in the tissues, tends to support this hypothesis.

3. Both the preceding theories could account for the precipitation of calcium from serum if the diffusible calcium was at or near the saturation point. Consequently the factors that allow the diffusible calcium to attain the saturation point are of distinct importance. In this

19. Bulger, H. A.; Dixon, H. H.; Barr, D. P., and Schregardus, O.: J. Clin. Investigation **9**:143, 1930.

20. Hess, A. F.; Benjamin, H. R., and Gross, J.: J. Biol. Chem. **94**:1, 1931.

regard a rather complicated situation is seen to exist, and as yet there is no absolute proof for the following hypothesis, but as there is much evidence that points in its direction it was thought advisable to present it.

It should be remembered that there is not necessarily a relationship between the level of the total serum calcium and the precipitation of calcium from the serum; that is, calcifications do not necessarily appear to result from hypercalcemia. Shelling [21] observed that parathyroidectomized rats more readily show calcifications following excessive administration of vitamin D than do normal rats. On the other hand, although the level of the total serum calcium does not appear to bear a distinct relationship to the development of calcifications, there may be a very close relationship between the level of the diffusible calcium and the institution of calcifications. There is good reason to believe that the nondiffusible and the diffusible calcium do not keep their normal relationships in hypercalcemia (Morgulis and Perley [22] and others), as during the attainment of hypercalcemia there appears to be a shift of calcium ions from the diffusible to the nondiffusible and also a shift from the intestine or bones to the diffusible, so that both are raised, but the greater increase is in the nondiffusible calcium. When, however, hypercalcemia is attained, if there is no further administration of parathyroid hormone or Vitamin D, the nondiffusible calcium begins to break down, and this break-down could easily be accompanied by a rather steady release of calcium ions, which could quickly bring the diffusible calcium to the saturation point and beyond this point result in precipitations (Ham [18]). Thus it is entirely possible that calcifications would most readily occur on the down-swing of the serum calcium curve. This hypothesis could explain the calcifications being produced in parathyroidectomized animals more readily than in normal animals, because the fall of the temporarily increased serum calcium would be greater than it would be if the animal had a stable parathyroid mechanism. It also could explain the latent period that occurred before the onset of calcifications following one single dose of irradiated ergosterol in both Laas' experiments and the ones reported in this paper. This hypothesis would also indicate that oscillations of the serum calcium level would be more likely to result in calcifications than steadily maintained simple hypercalcemia. In other words, it seems not unlikely that there is a possibility of the diffusible calcium being kept close to the saturation point, as the serum calcium is falling from a hypercalcemia peak by a continued release of ions from the nondiffusible calcium, and any condition that would allow for saturation of

21. Shelling, D. H.: Proc. Soc. Exper. Biol. & Med. **28**:303, 1930.
22. Morgulis, S., and Perley, A. M.: J. Biol. Chem. **88**:169, 1930.

the serum with diffusible calcium would allow calcifications to ensue not only by the previously described mechanisms but also by the process in itself.

The rather characteristic lesions produced in both the arteries and the cardiac musculature (fig. 4), it is thought, are best explained by the rather massive amounts of calcium that are deposited. On the other hand, one must remember that the administration of vitamin D in enormous amounts could first cause a withdrawal of calcium from the bones and possibly other tissues into the blood. There appears to be good reason to suspect that the calcium metabolism of cells could be considerably disturbed not only during the deposition of calcium, but also in the period of withdrawal antecedent to the deposition. In the sections studied in this work, the obvious lesions were always associated with a deposition of calcium, and the early degenerative signs described by many authors were not obvious. On the other hand, it is admitted that the rather severe methods used in this work were conducive to marked lesions, and it is possible that by adjusting dosages and intake of calcium lesions could be produced by the withdrawal of calcium from tissues during the phase of the rise in the blood calcium level. It is, of course, well known that the reaction of the cells of bone in response to a withdrawal of calcium from the matrix by parathyroid hormone or irradiated ergosterol is marked, so that tissue changes in other cells of the body could logically be expected. In this work, however, the well marked lesions were the edematous calcium-containing area between the elastic fibers in the aorta, with degeneration and calcification of both cells and fibers, the calcification of the wall of the coronary vessels, and zones of calcification and inflammatory cell infiltration in the cardiac muscle.

It appears interesting that a picture of myocarditis can be so readily produced by disturbing the calcium metabolism. Of course, these areas of inflammatory cell infiltration are associated with depositions of calcium, but there is a possibility that with less severe doses the inflammatory patches might be produced without such obviously large amounts of calcium. The predominant cells in the exudate are large mononuclears, and there are on occasion polymorphonuclear leukocytes. There is a marked tendency for the lesions to be situated about the coronary vessels.

SUMMARY

Enormous single doses of irradiated ergosterol will produce massive calcifications in the aorta, coronary vessels and cardiac musculature of the rat as soon as forty-eight hours after administration. Sections from the tissues twenty-four hours after administration show nothing that would presage such an imminent catastrophe, so that the calcifications

do not appear to depend on degenerative changes in the recipient tissues. On the other hand, the rapidity of formation, together with the massiveness of the calcifications, suggests very strongly that the prime factor in their causation is the inability of the serum to retain all its calcium in solution. It is suggested that precipitation depends on saturation of the serum with diffusible calcium plus other factors. These could be a change in carbon dioxide tension, the addition of other ions which would force a precipitation of calcium salts, or a continued liberation of ions from the nondiffusible calcium after the diffusible calcium had reached the point of saturation. It seems probable that conditions suitable for precipitation could be more easily obtained as the serum calcium level is falling after the attainment of hypercalcemia.

A marked inflammatory cell infiltration developed about the affected coronary vessels and about the calcified areas of cardiac muscle.

The evidence indicates that the toxic action of vitamin D does not depend on a quality separate from that on which its therapeutic action depends, and that the vitamin does not necessarily possess a specific toxic effect on tissues, but that the calcifications of hypervitaminosis D can be explained by its action on the calcium metabolism.

It is also suggested that the calcifications of the variety that depend on the inability of the serum to retain all its calcium in solution depend for their causation to a greater extent on the level of the diffusible calcium than on the level of the total serum calcium.

It should be clearly indicated that the so-called toxic effect of vitamin D demonstrated in these experiments was obtained only with enormous amounts of the vitamin, and that the doses used were infinitely beyond those utilized therapeutically in the administration of cod liver oil or viosterol.

CONGENITAL CYST OF THE LUNG

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The first description of a case of congenital cyst of the lung has been accredited to Nicolaus Fontanus.[1] Since his time a number of cases have been reported, and upward of fifteen names have been proposed for the condition. While many of these are based on incorrect data, certain features stand out rather prominently. In the cases in which the cysts are large, death often occurs *in utero*, during infancy or at best usually before the age of 25 years. In those in which the cysts are not large the average age attained is 55 years and exceptionally 84 years (Buchman[2]), although death may occur in infancy owing to rupture of a small cyst with resulting pneumothorax (Miller[3]). The condition may involve only one or both lungs, or a whole lobe or a part of one, or it may spring from the parietal pleura entirely unassociated with pulmonary tissue. There may or may not be a demonstrable connection with the bronchial tree (Pappenheimer[4]). There may be an associated malformed artery (Rosenthal[5]), hemihypertrophy of the body (Arnheim[6]) or neoplasia (Heller[7]) and the distended bronchi may or may not be pigmented. The presence or the absence of cartilage in the walls of the bronchi and the character of the epithelial lining have been utilized as points in determining the intra-uterine time at which the error in development occurred. The cystic cavities in Dustin's case were lined by multinucleated giant cells.[7a] Careful study of the reported cases utilized in classifications shows that there is little basis for subdividing them.

From the Pathological Laboratories of the Jefferson Medical College and Hospital, aided by the Martin Research Fund.

1. Meyer, H.: Virchows Arch. f. path. Anat. **16**:78, 1859. Bartholinus, Thomas, cited by Malpighi, Marcello: Opera omnia seu thesaurus locupletissimus botanico-medico-anatomicus, viginti quatuor tractatus complectens et in duos tomos distributus (complete works), Leyden, P. van der Aa, 1687, vol. 2, p. 349.
2. Buchman, E.: Frankfurt. Ztschr. f. Path. **8**:263, 1911.
3. Miller, R. T.: Arch. Surg. **12**:392, 1926.
4. Pappenheimer, A. M.: Proc. New York Path. Soc. **12**:193, 1912.
5. Rosenthal, S. R.: Arch. Path. **12**:387, 1931.
6. Arnheim, G.: Virchows Arch. f. path. Anat. **154**:300, 1898.
7. Heller, A.: Deutsches Arch. f. klin. Med. **36**:189, 1884-1885.

7a. Dustin, A. P.: Arch. de biol. **42**:229, 1931.

Many have been so poorly studied that only outline descriptions exist, and because of the ambiguity of these the cases have readily lent themselves to such classification. Congenital cysts generally come to autopsy unrecognized or undiagnosed (Koeckert,[8] Müller[9]). The following case is presented because of the association of an interesting physical sign and also because the opportunity of making a detailed morphologic study of the affected area was utilized.

REPORT OF CASE

Clinical History.—A white woman, aged 54, entered Jefferson Hospital, in the service of Dr. Burgess Gordon, on Nov. 21, 1930. She had always been strong and healthy and had worked hard as a housewife and as a domestic servant. Her best weight had been 150 pounds (68 Kg.), eighteen years before her admission to the hospital. During her entire life she had coughed and expectorated moderately. She was not subject to acute respiratory infection, although epistaxis had been fairly frequent. During the past three years she had been a patient in three hospitals because of gradually developing weakness, loss of weight (42 pounds [19.1 Kg.]), increased cough and several heart attacks characterized by palpitation, precordial pain, dyspnea and syncope.

There was deepening of the supraclavicular and infraclavicular fossae; the ribs and sternum were prominent. The chest was flat, more so on the left, and expansion was limited throughout. There were patchy areas of dulness and hyperresonance, also of increased and decreased fremitus. The breath sounds were roughened, prolonged and in places cavernous. Whispering pectoriloquy was heard over several small areas. A mixture of fine and coarse crackling and musical râles was widespread. A sound identical with a pleural friction rub was heard over the entire chest wherever the stethoscope was placed. Respirations averaged between 28 and 40 per minute. The fingers were clubbed, and there was a slight scoliosis involving the lower dorsal and upper lumbar vertebrae. The heart was rapid, impulse feeble; the sounds were muffled except the second pulmonic beat, which was accentuated. The blood pressure was 110 systolic and 60 diastolic. The pulse beats averaged 110 per minute. Occasionally there was pyrexia.

The urine was normal. No tubercle bacilli were found in the sputum. The hemoglobin content ranged from 75 to 105 per cent; the red blood cells were from 4,200,000 to 5,320,000 per cubic millimeter; the color index was 0.9; the white blood cells averaged about 6,000 per cubic millimeter, with a normal differential count. The Wassermann and Kahn tests were not made.

The roentgen films of the chest were described as showing a general involvement of both lungs, which appeared as though thickly sprinkled by small lumps of raw cotton. The bronchial tree was made out with difficulty. The appearance was considered to be that of generalized pulmonary tuberculosis. In another report, the changes were described as follows: "There is a tuberculous infection involving both lungs with cavities at the right apex. Throughout the rest of the right and in the lower three fourths of the left lung there are numerous exudative foci. From the x-ray point of view the lesion is undoubtedly chronic and long standing, but it is not well healed."

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8. Koeckert, H. L.: Am. J. Dis. Child. **17**:95, 1919.

9. Müller, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, p. 557.

The diagnosis of pulmonary tuberculosis was made in all the hospitals. Other diagnoses were chronic bronchitis, bronchial asthma and chronic myocarditis.

Death occurred on Jan. 20, 1931, during an attack of acute cardiac insufficiency complicating pneumonia.

Postmortem Examination.—The pleural surfaces were glistening and not adherent (fig. 1). Just beneath and showing through the visceral layer were round, gray, slightly elevated, sharply circumscribed nodules averaging from 1 to 3 mm. in diameter. The intervening depressed tissue (from a fraction of a mil-

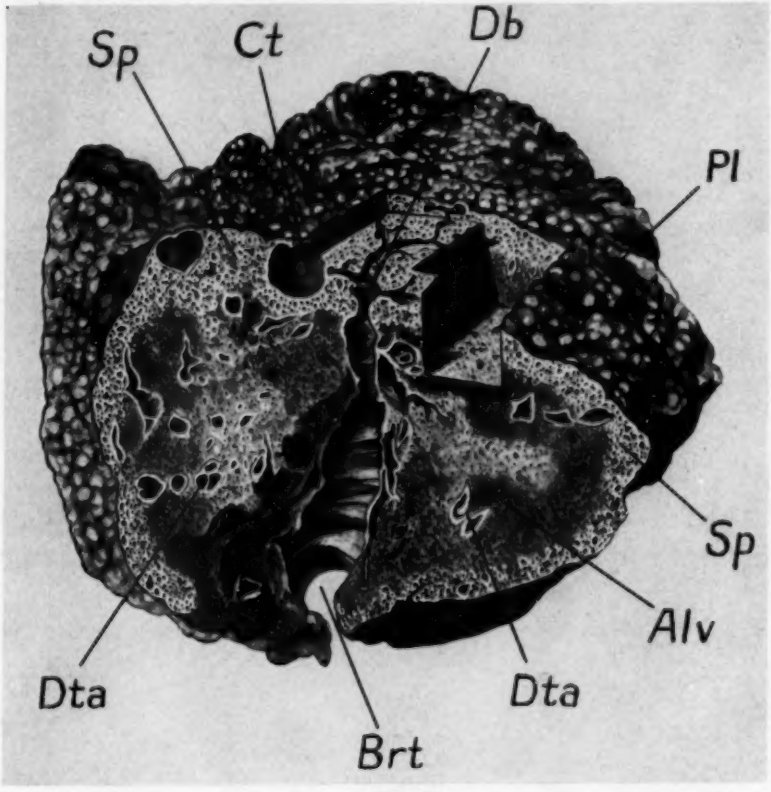

Fig. 1.—Drawing of the lung: *Pl*, pleural surface; *Sp*, subpleural band showing distended bronchi and stroma; *Brt*, dissection of distended bronchus and its branches, showing its subpleural ramification distal to *Db*; *Ct*, large, smooth-lined, cystlike cavity; *Dta*, distended bronchi lying among alveoli, *Alv*.

limeter up to 4 mm. wide) was sclerotic and airless. The nodules were numerous, the picture simulating somewhat that of miliary tuberculosis or that of widespread neoplastic metastases. The lungs cut with increased resistance. On section, these nodules were found to be thick-walled cavities. There were a few subpleural elevated, smooth-lined, thin-walled cysts measuring up to 15 mm. in diameter. Some of these contained as many as five openings, while in others, despite the most careful search, none could be demonstrated. Immediately beneath the pleura, distributed uniformly around the periphery of both lungs, was a layer varying in

thickness from a few millimeters to 3 cm., which was firm and mottled gray and dark red. It consisted of fibrous tissue in which cavities were present. These cavities varied in size from smaller ones barely visible without a magnifying glass to the larger ones already described. On careful dissection it was possible to follow some of these for a considerable distance in various directions. Proximally some communicated with the main bronchial tree. Distally they extended through the fibrous area to the under surface of the pleura, where they ramified parallel or tangential to it. They ended blindly or in a branch too small to be followed. The lumina of these distended bronchi were irregularly widened and narrowed and partially occluded with thick, gray, tenacious mucus. The mucosa everywhere lay

Fig. 2.—Lung. The pleura can be seen at the bottom of the photomicrograph. The character, contents and lining of the distended bronchi and the nodular accumulations of small round cells in the vascular connective tissue are shown; × 100.

in fine annular folds. Proximal to this subpleural bandlike area, the lung was consolidated with a recent pneumonic exudate. The bronchi showed cylindric and fusiform dilatations and appeared to be increased in number. The right lung measured 21 by 16 by 6 cm. and weighed 690 Gm. The left lung measured 22 by 18 by 6 cm. and weighed 720 Gm.

Other findings (confirmed by microscopic examination) were: hypertrophy of the right side of the heart (8 mm.), acute myocardial degeneration, hyperplasia of the splenic follicles, parenchymatous degeneration of the kidneys, acute membranous

and ulcerative colitis with melanosis, cholelithiasis, chronic cholecystitis, edema of the lower extremities and passive congestion of the viscera.

Sections were fixed in 10 per cent formaldehyde, Zenkers' fluid and Klotz' solution. They were blocked in celloidin and paraffin and cut at thicknesses varying from 5 to 200 microns. They were stained with hematoxylin and eosin, van Gieson's and Mallory's connective tissue stains, Verhoeff's elastic tissue stain, Mayer's muchematein stain for mucin, Gram's stain for bacteria in tissues, phosphotungstic acid for fibroglia and Levaditi's stain for spirochetes.

Microscopic Examination.—The bandlike layer lying immediately beneath the pleura consisted of various-sized, distended bronchi surrounded by an airless vascular connective tissue, containing small round cells (fig. 2). The distended bronchi varied in diameter from several microns to 15 mm., the majority averaging between 0.5 and 1.5 mm. They were round or oval or sometimes much distorted. They showed irregular, redundant serrations and papillary projections. Acute constrictions appeared in those cut longitudinally. Small budlike sacculations were observed, with invagination of the mucosa and multilocular cystlike formation. The lumens of about half of the bronchi were empty. Others contained desquamated epithelium, and still others were plugged with a stringy, hyaline material, which gave the staining reaction for mucin. In the meshes of this could be seen a few neutrophils, eosinophils and a shreddy granular material which appeared like cast-off cilia. The lamina propria was absent in most of the bronchi, while in others it consisted of varying amounts of connective tissue containing collagen and heavy elastic fibrils. The bronchi were lined by squamous, cuboidal, simple and pseudostratified, ciliated and nonciliated columnar epithelial cells. Transitions from one to the other were not uncommon in sections of single bronchi. Only rarely were mitotic figures encountered. Epithelial desquamation was widespread, and frequently the entire lining was separated *en masse*. In some places where desquamation had occurred, bare muscle fibers projected into the lumen. The walls of most of the distended bronchi were free from glands and pigment. They varied considerably in thickness, and were made up of cellular and hyalinized connective tissue, elastic fibers, cartilage and smooth muscle. Elastic tissue was present in the larger ones and appeared as one or more heavy layers just beneath the epithelium. The muscle in many was proportionately increased in amount, although in some it did not completely encircle the wall. Where cartilage plates occurred, they were for the most part in the walls of the larger bronchi. Some were encountered in the smaller ones, and a few appeared to be lying free in the interstitial tissue unassociated with bronchi. The latter occasionally occupied a position immediately underneath the pleura. In general, the plates were round, oval or crescentic. A representative one measured 1 by 10 mm. Many were composed of adult cartilage cells in normal arrangement. Others consisted of palely and deeply stained cells irregularly disposed in various-sized lacunae. At times the periphery became fibrocartilage and merged insensibly with the surrounding stroma. A few were partially calcified.

The stroma of the bandlike subpleural layer was made up of vascular connective tissue containing carbon pigment, smooth muscle and diffuse and focal accumulations of round cells indistinguishable from small lymphocytes. The connective tissue consisted of young and old fibroblasts separated by an abundance of collagen, fibroglial fibrils and elastic tissue. The muscle that was observed in the interstitial tissue was shown by serial sections to connect in many instances with the hypertrophied walls of the distended bronchi. The vascularization of this atelectatic portion was unusually excessive. For the most part, the vessels consisted of thin-walled, endothelium-lined tubes having the appearance of sinusoids rather than

capillaries. The arteries below 2 mm. in diameter showed a uniform subendothelial hyalinization with some atrophy of the media. The internal elastic lamina was unchanged except for occasional slight atrophy. A few of the arteries were occluded by fresh thrombi. There was no inflammatory cell infiltration, new formation of capillaries or thickening of the vasa vasorum in the coats of the vessels. The arterial sclerosis was neither of the hyperplastic (Rosenthal [5]) nor of the syphilitic (Arrillaga [10]) variety.

The pleura was not thickened. Its mesothelial cells were intact and normal. There was no exudate on it. The irregularity of the surface noted grossly resulted from small adjacent clusters of distended bronchi bulging the pleura outward. The depressions were due to the contraction of the intervening connective tissue. If tubules had been substituted for the bronchi, the picture would have corresponded to that of the renal surface in chronic glomerulonephritis.

The lung proximal to this subpleural atelectatic area consisted of normally formed alveoli, which were filled with an acute pneumonic exudate. There was some overgrowth of the stroma, and small distended bronchi similar to those described in the subpleural portion were occasionally encountered. The walls of the larger bronchi were hypertrophied and fibrotic.

A portion of the left lung was reconstructed in the following manner: A block of tissue was cut out so as to include a piece of pleura 12 by 5 mm. and the lung medially for a distance of 34 mm., including bronchi large enough for their connection with the main bronchial tree to be made out grossly. This piece of lung, which had been preserved in Klotz' solution, was dehydrated and infiltrated with parloidin. One hundred serial sections, each 50 microns thick, were cut in such a way that a strip of the pleura and all the structures beneath it for a distance of 34 mm. were present on each slide. The parloidin was removed; sections were stained with hematoxylin and eosin and mounted in balsam. The slides were numbered serially and studied carefully under the microscope. By means of a projectoscope, sections were magnified eighteen times, and the image was thrown on white blotting paper the average thickness of which was 0.9 mm. A tracing of each bronchus was then made and left unstained. The alveoli were drawn in solid blocks and stained red. The interstitial tissue and blood vessels were disregarded, so that in the model they appear as vacant spaces. The alveolar and bronchial tracings were cut out with a sharp knife and mounted serially (Miller,[11] Schaeffer [12]).

The finished model (fig. 3) measures 61.2 by 21.6 by 9 cm. It consists of two portions. The smaller extends proximal from the pleura for an average distance of 11 cm. and is a reproduction of the subpleural distended bronchi and connective tissue (fig. 4). The larger portion, occupying the remainder, averages 50 cm. in length, and reproduces alveoli, bronchi and connective tissue. From a study of these two parts the origin, structure, course and termination of the subpleural distended bronchi and their relation to functioning alveoli can be determined.

According to the model, the majority of the distended bronchi originating within the block of tissue studied were branches of a bronchus in continuity with the main bronchial tree (fig. 4 *Br*). Where branching occurred, the parent bronchus regularly underwent a saccular dilatation (figs. 1 *Db* and 4 *S*). Two groups of distended bronchi had no bronchial or alveolar connection. They occupied a position

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10. Arrillaga, F. C.: Cardiacos negros, Buenos Aires, Philadelphia, Wistar Institute Press, 1925.

11. Miller, W. S.: Anat. Rec. **48**:191, 1931.

12. Schaeffer, J. P.: Anat. Rec. **5**:1, 1911.

Fig. 3.—Photograph of a reconstruction model of distended bronchi and other structures for a distance of 34 mm. from the pleura (model is 61.2 cm. long).

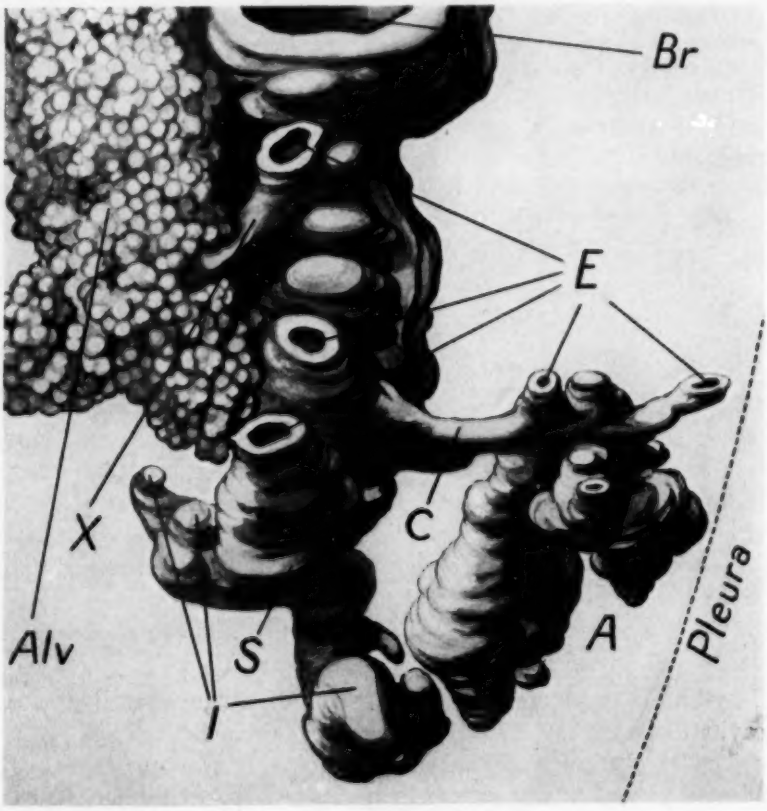

Fig. 4.—Drawing of a reconstructed group of distended bronchi in continuity. They lie immediately beneath the pleura, represented by the dotted line. The group of alveoli (*Alv*) in the upper left corner are fed by the bronchus *X*. *E* indicates bronchi, the lumens of which appear open to represent their termination beyond the block of tissue reconstructed; *I*, bronchi that end within the block of tissue reconstructed; *C*, a small connection between the parent bronchus *Br* (in continuity with the main bronchial tree) and the group of distended bronchi at *A*; *S*, a saccular dilatation.

each point of which was at a sufficient distance from every other bronchus that, had connections been present, they should have been demonstrable.

The progressive gradual tapering was not reproduced with the fidelity that is characteristic of the normal bronchial tree. On the contrary, these bronchi were characterized by coarse dilatations and constrictions as they progressed distally. This distorted them in such fashion that they were frequently narrower at the point of origin than they were some distance away. In addition, there was a fine irregularity which was manifested as a difference in diameter in each successive section of the same bronchus.

For the most part, the subdivisions ran at right angles or parallel to the parent bronchus, either in the same or in the opposite direction. At the periphery, their course tended to parallel the pleura. At variance with this, some described a circular course, some made an acute angle with the parent bronchus and others struck the pleura at a tangent.

A few terminated in functioning alveoli (fig. 4 *x*). The remainder ended blindly, usually in a saccular dilatation, less frequently without any change in the diameter of the lumen and occasionally in a tapered point. Those that terminated in functioning alveoli and those that ended blindly had identical origins.

The bronchi in the proximal portion of the model, while not showing such marked departures from normal, had many of the characteristics of the subpleural distended bronchi. They had small saccular dilatations in their walls, and fine and coarse irregularities in their diameters. They were much larger and more numerous and terminated more abruptly than was normal. Chiefly they supplied functioning alveoli, but occasionally they gave rise to distended bronchi similar in all respects to those found immediately beneath the pleura.

COMMENT

The significant symptoms in this case were the cough and the expectoration of life-time duration, due probably to irritation caused by the increased and unexpelled bronchial secretion. Several changes suggest themselves as responsible factors: the desquamation, the flattening of the lining cells with loss of cilia, the alternate constrictions and dilatations in the bronchi, the irregular distribution of the mural musculature, the absence of the tidal wave of air because of the failure of alveoli to form on the terminal bronchi and the interruption of adjacent alveolar contact by the interposition of excessive stroma, thereby abolishing collateral alveolar respiration (Lindskog and Van Allen [13]).

In addition to physical signs indicative of patchy consolidation and of cavitation, a curious sound was heard over the chest, which has been described as that of a pleural friction rub. It was not caused by a roughened pleura, as was proved by necropsy. Occurring as it did with each respiratory movement, it is of diagnostic importance. It may have depended for its production on sounds transmitted through the distended bronchi or on crinkling of the subpleural atelectatic area.

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13. Lindskog, G. E., and Van Allen, C. M.: Arch. Surg. **24**:204, 1932.

The roentgenographic changes were interpreted as due to pulmonary tuberculosis. The absence of symptoms comparable with such extensive involvement and the absence of bacilli in the sputum are to be regarded as important diagnostic points.

The associated sclerosis of pulmonary arteries and arterioles, hypertrophy of the right ventricle and polycythemia were interesting. The cardiac hypertrophy was undoubtedly secondary to the resistance offered by the fibrotic lungs and partly to the arterial sclerosis. Whether the sclerosis itself was due to the increased stress (Moschcowitz [14]) or to some other factor is difficult to decide. The polyglobinemia may have been compensatory for the lessened number of alveoli and also for the pulmonary arterial sclerosis (Weber and Bode [15]).

The cells in the subpleural bandlike area suggested an inflammatory reaction, a maldevelopment or a combination of the two. If inflammatory, the process was sufficiently intense that there should not have been the sharp localization over both lungs immediately beneath the pleura. Instead the pleura itself should have been involved, and the process should have converged on the hilus by extension along lymphatic channels. There was no true gummatous formation, but the arrangement of the small round cells into distinct nodules, the vascularity of the lesion and the arterial subintimal hyalinization suggested syphilis (fig. 2). It is more probable that this tissue was embryonic, representing arrested development of alveolar parenchyma, and that the excessive bronchial growth was the result of an attempt to complete this connection. A contributing factor was the normal postnatal bronchial growth (Wilson [16]), also the possible collapse of imperfectly or completely formed alveoli by the prolonged action of the same mechanism responsible for temporary alveolar collapse in asthma (Huber and Koessler [17]).

In the present case there were no signs of congenital syphilis. There was no history of any primary or secondary lesions or of prior administration of specific treatment. There had been no pregnancies. Wassermann and Kahn tests unfortunately were not made. After death neither characteristic gross nor microscopic evidences of the disease were found. No spirochete could be demonstrated in the sections from the lungs nor was the sclerosis of the pulmonary arteries syphilitic in nature. This evidence, while lacking in important essentials, is against

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14. Moschcowitz, Eli: Am. J. M. Sc. **174**:388, 1927.

15. Weber, F. P., and Bode, O. B.: Polycythaemia, Erythrocytosis and Erythraemia, London, H. K. Lewis & Co., 1929.

16. Wilson, H. G.: Am. J. Anat. **41**:97, 1928.

17. Huber, H. L., and Koessler, K. K.: Arch. Int. Med. **30**:689, 1922.

syphilitic infection. The presence or absence of syphilis is important because the frequency of visceral maldevelopment in this disease has led to its incrimination in the etiology of congenital cyst of the lung.

The demonstration in the gross specimen and in the reconstruction that certain distended bronchi were devoid of communication with the main bronchial tree confuses their origin. It is probable that at one time a connection existed and that it was later obliterated either by an inflammatory process or by traction of the interstitial connective tissue. Their increase in size would then depend on the pressure of the accumulating secretion which had no outlet.

SUMMARY AND CONCLUSIONS

In this case of congenital cyst of the lung, the majority of the distended bronchi communicated with the main bronchial tree. A few had no such connection, and they were therefore true cysts. Evidence is offered that these may have enlarged during postnatal life. The majority of the distended bronchi ended blindly. A few terminated in functioning alveoli. This accounts for the variation in their pigmentation.

As associated factors, hypertrophy of the right side of the heart, sclerosis of the pulmonary artery and polycythemia were found.

The physical sign observed, indistinguishable from a pleural friction rub, is of diagnostic import.

Until more information is available such malformations should be classified under the general term of "congenital cyst of the lung."

EXPERIMENTAL PATHOLOGY OF THE LIVER

XI. THE EFFECT OF PHOSPHORUS ON THE NORMAL AND ON THE RESTORED LIVER FOLLOWING PARTIAL HEPATECTOMY IN THE ALBINO RAT

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Anderson [1] recently studied the effect of chloroform on the normal and on the rapidly restored liver, after partial hepatectomy, in white rats, and concluded that the restored liver was more resistant to the effects of chloroform than the normal liver. Lacquet,[2] using carbon tetrachloride, came to similar conclusions. This report concerns a comparable investigation in which I studied the influence of phosphorus on the normal and on the restored liver following partial hepatectomy.

The literature on the effect of phosphorus on the animal organism is probably more complete than that concerning the effect of either chloroform or carbon tetrachloride, and is somewhat older. Of late, phosphorus has not been used so much for experimental purposes, and since the substitution of the relatively inert red for the very active yellow phosphorus in the manufacture of matches, and since the decline in the use of the drug as a therapeutic agent, poisoning is not often encountered. In the following cursory review I shall cite only those more recent contributions to the literature which are pertinent to my study.

According to Luciani,[3] the epithelial cells of the gastro-intestinal canal (like the hepatic cells) have a protective as well as a secretory function. They are able to diminish or to inhibit the effects of toxic substances whether introduced from without or formed within the body. This phenomenon depends not merely on the slow rate at which alkaloids and other toxic substances are absorbed by the intestinal epithelium, but on the fact that after absorption they pass by the radicles of the portal system to the liver, where they are arrested by the hepatic cells, which store up the alkaloids in their cytoplasm, partly restoring them to the intestine with the bile and partly discharging them by the hepatic

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This work was done in the Division of Experimental Surgery and Pathology.

1. Anderson, R. M.: Arch. Path. **14**:335, 1932.
2. Lacquet, A. M.: Proc. Staff Meet., Mayo Clin. **5**:215, 1930.
3. Luciani, Luigi: Human Physiology, New York, The Macmillan Company, 1913, vol. 2, p. 331.

veins for elimination by the kidneys. Schiff [4] found that the fatal doses of narcotic poisons were much lower when introduced hypodermically than when injected directly into the portal vein.

Opie and Alford [5] studied the influence of diet, and found that phosphorus produced fatty degeneration, which was most advanced in the liver. They found that susceptibility to intoxication with chloroform is greatest after a diet of fat, less after one of meat, and least after one of oats and cane sugar. The fatty degeneration produced by phosphorus in the liver was also seen in the kidneys, heart and muscles. Although fat appeared to increase the toxicity of chloroform, meat with equal constancy increased the susceptibility to poisoning by phosphorus. Furthermore, chloroform produced necrosis at the center of each hepatic lobule, whereas phosphorus usually produced widespread fatty degeneration, more intense at the periphery. Phosphorus is less destructive to the hepatic cell, but when given in large doses and especially to animals on a diet of meat, it caused widespread necrosis, more marked at the periphery of the lobule.

Simonds [6] found that in phosphorus poisoning the liver was large and fatty, and that the fatty change began in the peripheral part of the hepatic lobule, but that actual necrosis occurred relatively late. Likewise in eclampsia, fatty degeneration and early necrosis began at the periphery.

The condition in which phosphorus reaches the liver to exert its toxic effect is not known. Plavac [7] (1904) concluded that phosphorus enters into some combination that acts as the poison. Ciaccio and Scaglione [8] studied the effect of chronic phosphorus poisoning on the mitochondria of the choroid plexus, and showed that the mitochondria lost their normal rod shape and became definitely granular.

Simonds found the liver to be the source of much of the intoxication in phosphorus and chloroform poisoning, as well as in acute yellow atrophy. The effects of phosphorus are not manifest until the second or the third day, that is, until the liver is free from glycogen. He suggested that the glycogen protects in phosphorus poisoning possibly by affecting the state of the colloids of the cells; first, by stabilizing the emulsion and preventing its "breaking," with the throwing out of droplets of fat, and second, by reducing the permeability of the cells to the poison.

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4. Schiff, M., quoted by Luciani,[3] p. 331.
5. Opie, E. L., and Alford, L. B.: J. Exper. Med. **21**:1, 1915.
6. Simonds, J. P.: Arch. Int. Med. **23**:362, 1919.
7. Plavac, V., quoted by Simonds.[6]
8. Ciaccio, C., and Scaglione, S.: Beitr. z. path. Anat. u. z. allg. Path. **55**:131, 1912-1913.

Bollman [9] stated that the liver is able to resist better the toxic destruction induced by chloroform, phosphorus, carbon tetrachloride and other drugs, provided it is rich in glycogen, and that more extensive lesions are produced if the liver has suffered previous injury.

METHODS OF INVESTIGATION

The white rat was used for this study because of the relative ease with which a large percentage of the liver may be removed and the rapidity with which it is restored after partial removal. The rat withstands partial hepatectomy very well, and no special preoperative or postoperative care is required. Infections are rather uncommon, and throughout the entire series of animals used, peritonitis was rarely encountered at postmortem examination. Dextrose solution was provided the day before and the day of operation in order to secure an adequate glycogen reserve. This enabled the animals to withstand the anesthetic and operation more successfully.

At operation, approximately from 65 to 75 per cent of the liver was removed according to the method described by Higgins and Anderson.[10] An aseptic technic was maintained during all the operations. After operation, all animals were returned to their respective cages, where they remained on the routine diet for one month, in order that ample time might be allowed for restoration of the liver.

In order to determine the toxic dose and the minimal lethal dose of yellow phosphorus for the normal rat, uniform conditions of diet and caging were maintained. Since glycogen is known to offer certain protection, it was necessary that the glycogen content of these livers should be relatively low. In administering phosphorus in the morning prior to feeding, I was assured that the glycogen would be at a minimum. A series of normal rats of approximately the same weight and age were caused to fast for eighteen hours, and were then used in determining the minimal lethal dose of yellow phosphorus for the normal animal. Varying doses of yellow phosphorus in oil (yellow phosphorus in 1 per cent solution of refined cottonseed oil) were injected into the subcutaneous tissues of the abdominal wall. By killing these animals in groups at certain intervals after injection and studying their livers, and by observing mortality among them, it was found that 4 mg. of phosphorus for each 100 Gm. of body weight was the dose of phosphorus that would consistently produce hepatic lesions in normal rats and yet not induce high mortality.

A group of normal rats on the routine diet also were killed in the morning before feeding.

Tissues from all the livers were fixed in two solutions. The tissues selected for fat, connective tissue, hematoxylin-eosin and mitochondrial stains were preserved in 10 per cent neutral formaldehyde, and tissues selected for the del Rio Hortega technic were fixed in an iron and alum solution.

Since phosphorus is excreted from the liver through the bile and reabsorbed from the intestinal tract (Adami [11]), I studied a series of rats in which the common bile duct had been ligated, thus inducing obstruction. One animal was killed seventy-two hours and another one week after the ligation to serve as controls on cytologic changes. The remainder of the series was divided into two groups;

9. Bollman, J. L.: Proc. Staff Meet., Mayo Clin. **4**:369, 1929.

10. Higgins, G. M., and Anderson, R. M.: Arch. Path. **12**:186, 1931.

11. Adami, J. G.: The Principles of Pathology, Philadelphia, Lea & Febiger, 1910, vol. 1, p. 311.

in one group phosphorus was given forty-eight hours after operation, and in the other group, a week after operation. The livers were fixed, stained and studied as described, and the lesions produced were contrasted with those found in the normal animal as well as with those in the animal with the recently restored liver following partial hepatectomy.

THE EFFECT OF PHOSPHORUS ON THE NORMAL LIVER

In a series of fifty normal rats that received 4 mg. for each 100 Gm. of body weight and were killed in groups at intervals of one, two, three, four, five, six, twelve, eighteen, twenty-four, forty-eight, seventy-two and ninety-six hours and one, two, three and four weeks, the most outstanding effect in the liver was a

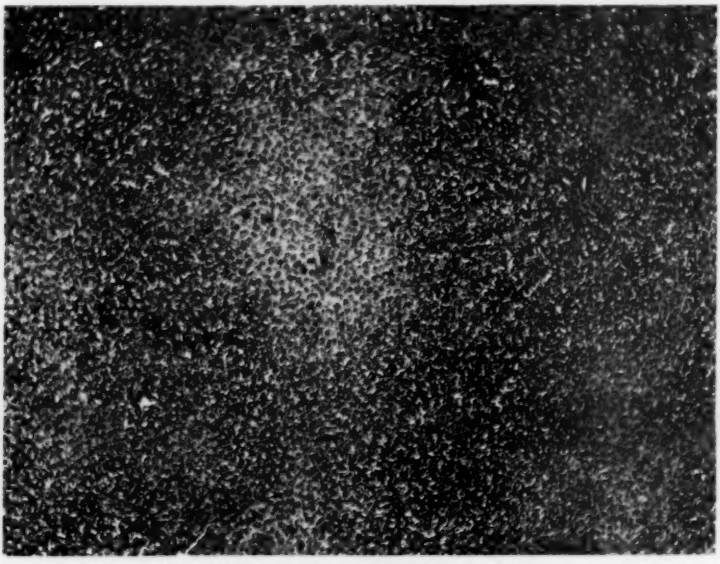

Fig. 1.—The liver of a white rat twenty-four hours after administration of phosphorus (hematoxylin and eosin; × 65).

fatty change. This fatty condition of the liver was observed on opening the abdomen, and at necropsy the amount of fat contained in the liver was estimated and recorded. The fat present was graded on a basis of 1 to 4. A liver in which the fat was graded 1 was considered practically normal, but was slightly yellow on very close inspection, whereas a liver in which the fat was graded 4 was definitely and unmistakably fatty and had the yellow appearance found in the liver of an animal dead of phosphorus poisoning from seventy-two to ninety-six hours after injection.

The animals varied slightly in their reactions to phosphorus in spite of the precautions taken to maintain uniform conditions. The first definite changes in the liver were noted twenty-four hours after the phosphorus was given (fig. 1). The fat, visible microscopically, occurred at the periphery of the lobule and was uniformly distributed in the cell in the form of small droplets.

The normal liver usually contains some fat, which has no characteristic distribution within the lobule, but is scattered here and there in a few cells. Such fat

distribution found either in the normal animals or in the series of animals that received phosphorus was graded 1. In a liver in which the fat was graded 4, every parenchymal cell was heavily laden with fat.

Twenty-four hours after phosphorus had been administered, the fat content of the liver was usually graded 1 or 2. The nucleus was in the center of the cell, or it was crowded to the periphery near its membrane, and there was moderate vacuolization of the cytoplasm of the cells at the periphery of the lobule. There was also slight to moderate cellular infiltration. At forty-eight hours there had been a slight increase in the extent of the injury. The liver contained more fat, and there was more marked cytoplasmic vacuolization (fig. 2). Some cells had been completely destroyed, and the wandering cells about the cell débris were

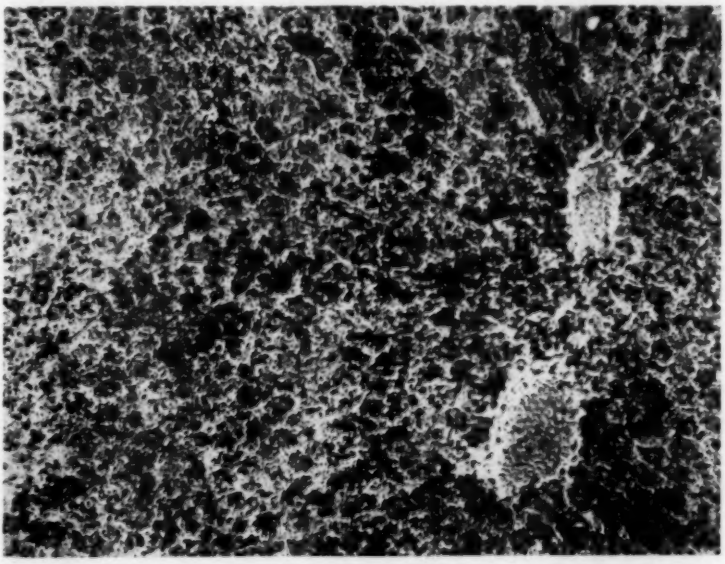

Fig. 2.—The liver of a white rat forty-eight hours after administration of phosphorus (sudan III; × 175).

definitely infiltrating cells. The mitochondria were for the most part granular, decreased in number and equally distributed throughout the cytoplasm.

The most marked changes occurred at seventy-two hours, when the lesion was at its height (fig. 3). Every cell in the hepatic lobule was involved, and the liver for the most part contained fat graded 2 or 3. The fat still appeared most pronounced at the periphery of the lobule, and the hematoxylin and eosin stains disclosed extensive and marked vacuolization of the cytoplasm up to the region of the central vein; in one case every cell was involved. There was cellular infiltration, which was more accentuated in regions in which some of the hepatic cells had been destroyed. Many mitotic figures were seen.

At ninety-six hours, the liver both grossly and microscopically was less fatty than at seventy-two hours. The fat nearest the central veins had disappeared, and the necrotic cells were being replaced by new hepatic cells. Many mitotic figures were still seen. There were considerably fewer mitochondria than normally, and they still appeared as large granules (fig. 4).

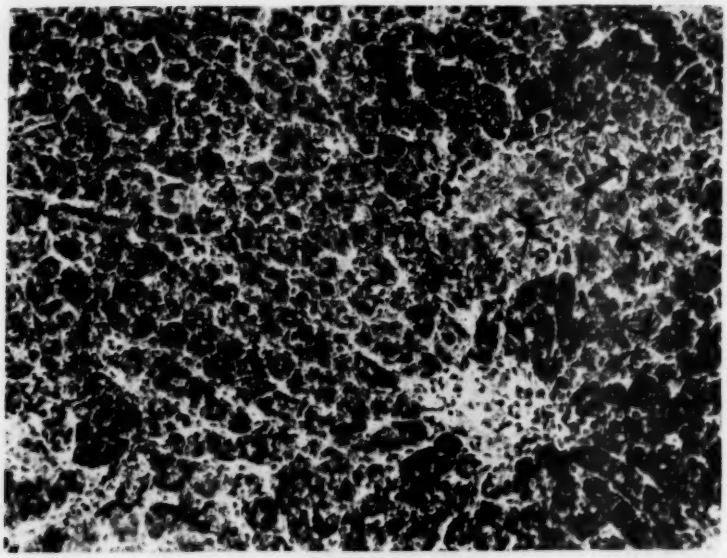

Fig. 3.—The liver of a white rat seventy-two hours after administration of phosphorus (sudan III; × 175).

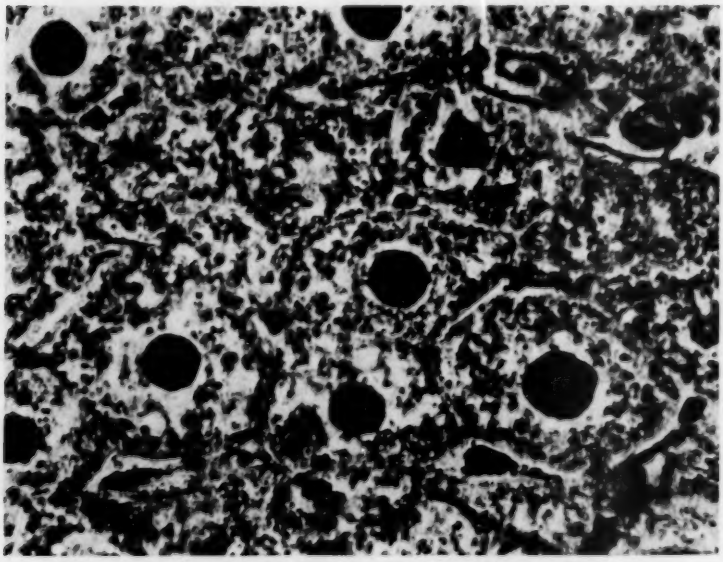

Fig. 4.—Mitochondria in hepatic cells of a white rat ninety-six hours after administration of phosphorus (del Rio Hortega; × 100).

At one week, the liver had essentially returned to a normal condition; most of the fat had been removed, the necrotic cells had been replaced, and the mitochondria again appeared as fine rods and fine granules. At two, three and four weeks, the livers continued normal in every respect.

THE EFFECT OF PHOSPHORUS ON THE RECENTLY RESTORED LIVER FOLLOWING PARTIAL HEPATECTOMY

Four milligrams of phosphorus for each 100 Gm. of body weight was given to a series of fifty rats following restoration of the liver after partial removal, and the animals were killed in groups at one, two, three, four, five, six, twelve, eighteen, forty-eight, seventy-two and ninety-six hours and one, two, three and four weeks

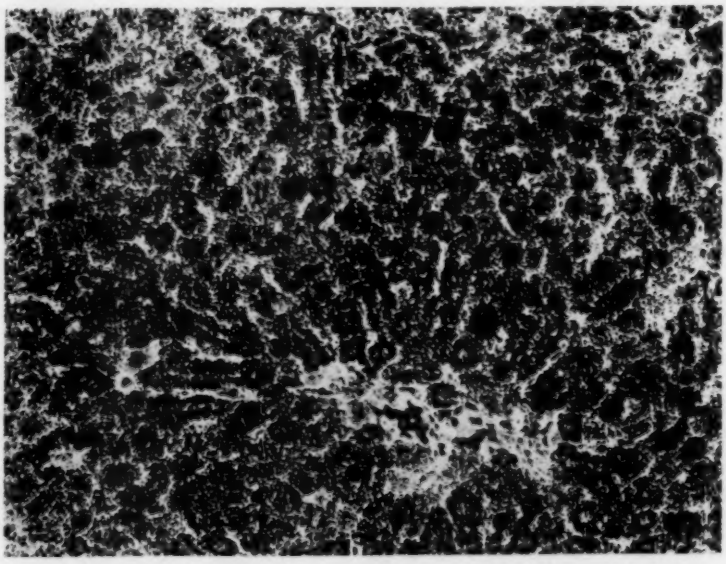

Fig. 5.—The liver of a white rat four weeks after partial hepatectomy and eighteen hours after administration of phosphorus (sudan III; × 175).

after injection. Their livers were studied grossly and microscopically, and the extent of injury was estimated in a manner comparable to that employed for normal animals.

Prior to twelve hours after injection, the animals, with one exception, did not reveal gross or microscopic evidence of a greater deposition of fat than that in the control group. At twelve hours, the fat in the livers of three of the four animals killed was graded *2*; the liver of the fourth animal appeared to be normal at eighteen hours (fig. 5). There were slight congestion, some vacuolization and infiltration; the changes were most noticeable at the periphery, and the fat content was graded *2* or 3. The mitochondria were small rods and small granules, but they were apparently somewhat larger than those seen in the normal animal.

At twenty-four hours there was only a slight change from the conditions seen at eighteen hours (fig. 5), and at forty-eight hours conditions were the same, except that the lesions were more extensive and vacuolization of the cytoplasm was more marked. Mitotic figures were already numerous.

At seventy-two hours, the lesions were most marked. The fat in all the livers was graded 3 or 4, and there was extensive vacuolization of the cells, which involved those adjacent to the central vein as well as those at the periphery. There was moderate infiltration by wandering cells, and mitosis was common.

At one week, the fat content of the livers of three of the five animals killed was normal, and cytoplasmic vacuolization was slight. Mitotic figures were numerous, and the mitochondria had returned to normal. The fat in the livers of the other two animals was graded 2.

THE EFFECT OF PHOSPHORUS ON THE LIVER FOLLOWING LIGATION OF THE COMMON BILE DUCT

Fifteen normal rats were subjected to obstruction of the common bile duct. The effect of phosphorus on the livers of these animals was studied at intervals ranging from six hours to one week after injection. One group of seven animals received injections of phosphorus forty-eight hours after the common bile duct had been obstructed, and another group of six animals received injections at the end of one week after the operation. One animal was killed seventy-two hours and another one week after operation.

At necropsy, the animals were markedly jaundiced. The peritoneum, liver, kidneys and muscles were distinctly yellow. One week after operation, the extrahepatic ducts and the common bile duct proximal to the ligature were enormously distended, so that the hepatic ducts had a transverse measurement about equal to that of a lobe of the liver. Forty-eight hours after operation, the bile in the ducts was yellowish, but that found at the end of a week was clear and watery. The livers of these animals were so discolored with bile pigments that it was impossible to estimate the amount of fat grossly. Microscopically, however, it was easy to distinguish the fat and to estimate the amount present.

The most striking feature noted in the stained sections of these livers was the marked increase in the number of the bile passages (fig. 6). The picture presented was entirely different from anything observed in the other groups studied. At each portal space there were, instead of the usual one or two, or possibly three, bile passages, a great many new ducts. These ducts were so numerous that in some lobules they extended well beyond the midzone. This description holds for the controls examined at forty-eight hours as well as for those examined at one week; the only difference was one of degree; that is, at one week after operation the extrahepatic ducts were larger and more distended and the contents clearer, and the increase in the number of periportal bile passages was more marked. The new bile passages were supported by very little connective tissue, and mitotic figures in the biliary epithelium were common. The epithelial cells and their nuclei were larger than those in normal livers. The cells of the parenchyma were normal, and there was no evidence of injury or of repair. The fat at seventy-two hours and at one week was graded 1. The droplets were of medium and large size and were scattered about the central vein.

The lesion produced by phosphorus in the livers of these animals in which the common bile duct had been ligated was identical in type and situation with that produced in the normal and in the recently regenerated livers, but there was a distinct difference as to the time of its appearance and the period of its height.

In the group in which injections were given forty-eight hours after ligation of the common bile duct, the lesion was present as early as six hours after the injections. The liver was jaundiced, and the fat was graded 2, with medium and large droplets of fat filling all the cells in the periportal zone. There was slight cellular

infiltration, and the mitochondria were of the large granular type. At twenty-four hours, the fat was graded 3, and the change was far more marked than at six hours. At forty-eight hours, the lesion was less, and the fat was graded 1.

At seventy-two hours, the lesion was similar to that at twenty-four hours, except that the cytoplasmic vacuolization was less pronounced. Mitotic figures were occasionally seen among the hepatic cells. At ninety-six hours and at one week after injection, the livers were again normal as far as could be determined, except that the mitochondria remained as large granules. In fact, in all animals in which the common bile duct had been ligated, the mitochondria were never normal before or after the administration of phosphorus. Likewise in the animals that were given injections one week after the ligation of the common bile duct, the lesion was well marked at six hours, and the sequence was more or less identical with that when phosphorus was given forty-eight hours after operation.

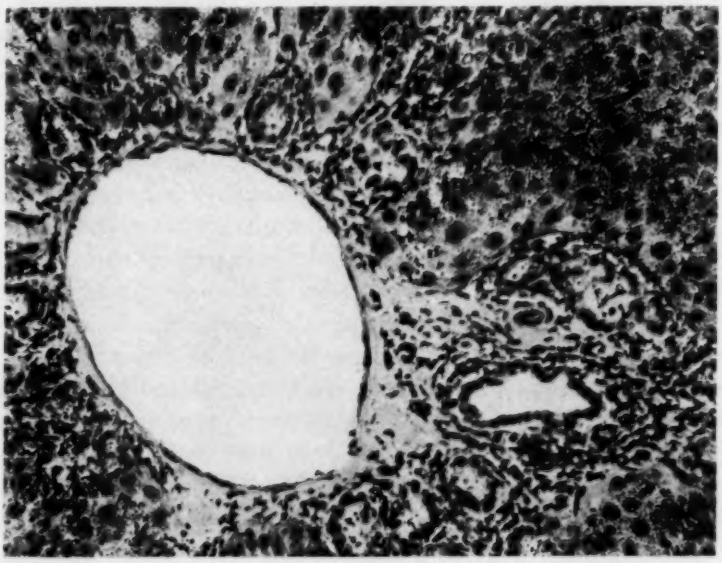

Fig. 6.—The liver of a white rat one week after ligation of the common bile duct and six hours after administration of phosphorus (× 175).

COMMENT

The amount of yellow phosphorus that I found would consistently produce lesions in the liver of the albino rat was much larger than the amount employed by other workers. The difference in response to a given poison is difficult to explain, although it is known that animals of the same experimental group vary considerably in their response to a given dose of phosphorus.

In the group of normal animals that received the injection, 4 mg. of phosphorus for each 100 Gm. of body weight, the lesion appeared between eighteen and twenty-four hours later at the periphery of the

lobule and gradually extended toward the center, attaining the height of injury at about seventy-two hours.

Necrosis and cellular infiltration were not as prominent a part of the lesion as in carbon tetrachloride poisoning, for example. The lesion consisted mainly of fatty change, which has been designated as fatty degeneration. There is much controversy as to whether this change is really degenerative or the result of infiltration. For the purpose of this study, however, the origin of this fat is irrelevant, since I was primarily interested in knowing whether the recently restored liver following partial hepatectomy differed essentially from the normal liver in response to phosphorus.

Seventy-two hours after injection, when the maximal injury had been reached, the process of repair had begun. The fat disappeared first from the cells at the center of the lobules, and the process of recovery proceeded toward the periphery. A week after injection, the liver had returned to normal. The hepatic cells were again normal in appearance and in fat content, and the mitochondria were fine rods and granules. There was no increase in connective tissue, and the normal structure of the liver was regained, so that there was no distortion or scar formation from any overgrowth of supporting tissue.

Although the fatty change characteristic of phosphorus poisoning appeared in the livers of normal animals twenty-four hours after the subcutaneous injection of phosphorus, it appeared within twelve hours after such an injection in rats with recently restored livers following partial removal. From this time on there was progressive extension of the lesion from the portal spaces toward the central veins, just as in normal animals that had received phosphorus. The most marked lesion, however, was observed at the same interval after injection of phosphorus as in the normal animal, namely, seventy-two hours; but the injury was more slowly repaired in the recently restored organ. At ninety-six hours there was scarcely any demonstrable change in the extent of the lesion, and even at one week after injection there were definite fatty changes in the livers of two of the five animals. At the end of four weeks, severe and extensive fatty change appeared in one animal, which was interpreted as the result of phosphorus poisoning.

After ligation of the common bile duct there was definite injury to the hepatic cells, as indicated by the effects on the mitochondria. The mitochondria, instead of appearing as fine rods and fine granules, were larger and fewer, and were concentrated about the nucleus of the hepatic cell.

After an injection of phosphorus in amounts corresponding to those used in normal animals and in those with recently restored livers, there was a marked difference in the response in the liver in which the common

bile duct had been obstructed. The action of the phosphorus was the same and in the same situation, but its extent, time of appearance and degree of healing varied widely from that observed in the normal and in the recently restored livers. The lesion appeared within six hours after injection, but it was never marked, and it had entirely cleared up by the end of ninety-six hours. The mitochondria, however, never returned to normal, which indicated that there was probably some injury to the cellular constituents of the liver after obstruction to the common bile duct and the resulting jaundice.

Thus the livers in which the common bile duct had been obstructed by ligation apparently were less susceptible to the untoward action of phosphorus. Although the lesion of phosphorus poisoning appeared sooner after injection in this series than in the normal or in the regenerated series, it never was as marked and did not persist as long. This is in keeping with the teaching of Adami, namely, that phosphorus is eliminated in the bile into the intestines, from which it may be reabsorbed, thus producing a vicious circle and prolonging the effect.

From my observations, it appears that the lesion produced by phosphorus in the recently restored liver of the albino rat develops more rapidly, is more extensive and is slower in repair than that induced in the normal liver. Thus, as far as the detoxification of phosphorus is concerned, it would seem that the recently restored liver is far less effective physiologically than the normal liver.

This conclusion is in contrast with the conclusions of Anderson, who used chloroform as the hepatolytic substance. He found that the recently restored liver was less susceptible to chloroform poisoning than the normal liver. In other words, he found that a given dose of chloroform would produce greater injury in the normal liver than in the recently restored liver. Likewise, Lacquet, while working with carbon tetrachloride, found that the recently restored liver was more resistant to chemical injury, in that the lesion produced was far less extensive and recovery ensued far more rapidly than in the normal liver. He found this to be true, however, only when the lesion was induced from two to four weeks after partial hepatectomy, when, as he pointed out, the hepatic parenchyma was exceedingly active and perhaps more embryonic in its qualities. The lesion induced two months after partial removal of the liver was more or less identical with that which Lacquet encountered in a normal liver after the administration of carbon tetrachloride.

I am unable to say whether the fat that appears in the liver after the administration of phosphorus is the result of a destruction of mitochondria, as has been stated by Cowdry (1926), or whether it arises from some other source. Certainly there are changes that take place in

the mitochondria at the time of or just before the fat becomes visible in the cells, but whether the fat originates in or from the mitochondrial substance, I am unable to determine. As the fat disappears the mitochondria return to their normal size and form.

CONCLUSIONS

Yellow phosphorus produces a characteristic lesion in the recently restored liver of the albino rat. This lesion cannot be distinguished grossly or microscopically from the lesion produced in the normal liver. It consists of a fatty change, which is always most marked at the periphery of the lobule.

The lesion produced in the recently restored liver by phosphorus makes its appearance sooner, becomes more extensive and is slower in its repair than that produced in the normal liver.

After the common hepatic duct has been obstructed surgically, the untoward or toxic effect of phosphorus on the liver is observed sooner, but the lesion produced is not so extensive as that produced by a similar dose of the drug in the normal or in the recently restored liver. Furthermore, the fatty change disappears in a much shorter time from the liver of an animal in which the common bile duct was ligated prior to the administration of phosphorus. There seems to be little difference whether the toxic drug is administered forty-eight hours or one week after the duct has been obstructed.

THE PARATHYROID HORMONE

ITS REGULATORY ACTION ON THE PARATHYROID GLANDS AND TOXIC EFFECT ON THE TISSUES OF THE RAT

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The effects of excessive doses of parathyroid hormone have been described by several investigators, and lesions of the skeletal system, produced by administration of the hormone, have been subjected to intensive study. It was not our plan to repeat these experiments, but rather to determine the acute effects of the hormone on the cells of the parathyroid gland. While the investigation was under way, one of us (W. R. Tweedy [1]) developed methods by which the hormone could be inactivated and the inert product partially reactivated. This suggested observations on the toxicity of the hormone not heretofore possible. Furthermore, it was found that a detailed study of hormonic lesions of the soft tissues of the rat had not been reported.

The first part of this paper deals with the action of the parathyroid hormone on the cells of the gland producing it, and the second part, with the pathogenesis of the lesions produced by the parathyroid hormone.

ACTION OF EXCESS PARATHYROID HORMONE ON THE CELLS THAT SECRETE IT

That compensatory hyperplasias, hypertrophies and regenerations are responses to physiologic needs is easy to demonstrate, although the mechanism by which these cellular changes are brought about is not clearly understood. Increased blood supply and increased functional demand are accepted as formative stimuli. Other and more specific factors in the regulatory mechanism must be recognized. Loeb [2] and his associates found that the feeding of thyroid inhibited regeneration

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The preparation of a portion of the hormone used in these studies was aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Tweedy, W. R., and Torigoe, M.: J. Biol. Chem. **48**:97, 1932.
2. Loeb, L.: J. M. Research **41**:481, 1920.

of the thyroid remnant after partial thyroidectomy. One of us (F. A. McJunkin [3]) demonstrated the inhibitory effect of insulin on the proliferation of the islet cells of the pancreas. We were therefore interested in making observations on the effect of parathyroid hormone on the parathyroid glandules.

Methods.—Histologic: The animals were killed at approximately eighteen hours after the last injection, and the tissues were immediately fixed. We soon found that formaldehyde was unsatisfactory for the fixation of the parathyroid glands of the rat, and that the best results could be obtained by fixing the two glandules, with the minimum amount of thyroid tissue about them, for two hours in a mixture consisting of 8 parts of 2.5 per cent potassium bichromate and 2 parts of 40 per cent aqueous solution of formaldehyde, after which they were placed in a 2.5 per cent potassium bichromate solution for two days. The entire glands, embedded in paraffin, were then cut into serial sections, 8 microns in thickness. With a mechanical stage, mitoses were enumerated, in most instances, in both parathyroid glands. Until experience was acquired, there was difficulty in the identification of certain of the karyokinetic figures. Animals kept on the same rations and in the same environment as the treated ones were used as controls.

Chemical: Before the animals were killed, blood was drawn by cardiac puncture, and the calcium analysis made, in most instances, on a 1 cc. sample of serum. The Kramer-Tisdall [4] method, as modified by Tweedy and Koch,[5] was employed.

An average blood serum value of 10.8 mg. per hundred cubic centimeters was found for twelve normal animals kept on the same rations as the treated animals. Some of the twelve appear as normal controls in the tables, and the others were selected at random. In previous work, one of us (W. R. Tweedy [6]) had found that the normal value for different rats may lie between 9.25 and 12.5 mg. per hundred cubic centimeters. We accordingly interpreted any value greater than 12.5 as above normal.

The hormone preparation designated "L" in the tables is para-thor-mone. The preparation not so designated was prepared by the method of one of us (W. R. Tweedy [7]) and standardized by Collip's procedure.[8] The acid alcohol inactivated hormone preparation is described by one of us [1] in a separate publication.

Information to show that a deficient supply of hormone in the tissues favors proliferation of parathyroid cells was obtained by Halsted,[9] who successfully transplanted parathyroid gland only in those animals in which one half of the parathyroid tissue has been previously removed. One of us (W. R. Tweedy [10]) obtained "takes" only when the blood calcium was below 8 mg. per hundred cubic centimeters.

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3. McJunkin, F. A., and Roberts, B. D.: Proc. Soc. Exper. Biol. & Med. **29**: 893, 1932.
4. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475, 1921.
5. Tweedy, W. R., and Koch, F. C.: J. Lab. & Clin. Med. **14**:747, 1929.
6. Tweedy, W. R., and Chandler, S. B.: Am. J. Physiol. **88**:754, 1929.
7. Tweedy, W. R.: J. Biol. Chem. **88**:649, 1930.
8. Collip, J. B., and Clark, E. P.: J. Biol. Chem. **66**:133, 1925.
9. Halsted, W. S.: J. Exper. Med. **11**:175, 1909.
10. Tweedy, W. R., and Chandler, S. B.: Unpublished data.

Excess hormone, on the other hand, was found by Jaffe and Bodansky [11] to cause atrophy and distortion of the parathyroid cells. In our animals we could not clearly establish either of these two histologic changes. We used the rat, not the dog, and our experiments were of shorter duration.

Effect on Mitotic Activity.—The average number of mitoses per animal in eight control rats was 37.7 (table 1). The action of the parathyroid hormone was decisive. The maximum rate in the animal that received the highest dosage of the hormone (table 2) was less than

TABLE 1.—*Mitoses in Normal Control Rats*

Rat	Weight, Gm.	Glands Counted	Mitoses per Animal	Blood Serum Calcium, Mg. per 100 Cc.
1	130	2	23	....
2	135	1	27	....
3	142	2	13	11.6
4	215	2	53	....
5	132	2	51	10.5
6	100	2	23	....
7	125	2	50	....
8	153	2	61	....

TABLE 2.—*Mitoses in Hormone-Treated Rats*

Rat	Weight, Gm.	Duration of Experiment, Days	Dosage, Units and Times Injected	Glands Counted	Mitoses per Animal	Blood Serum Calcium, Mg. per 100 Cc.
1	118	3	50 (3×)	2	2	17.1
2	130	7	50 (4×)	1	4	....
3	145	15	10 (12×)	2	3	11.4
4	130	15	10 (12×)	2	1	10.8
5	122	10	50 (3×)L	2	3	12.1
6	110	3	50 (3×)L	2	0	15.2
7	120	3	50 (3×)L	1	6	14.4
8	125	3	50 (3×)L	2	3	15.5
9	130	3	25 (3×)L	2	3	13.7
10	148	3	25 (3×)L	2	4	11.2
11	135	3	25 (3×)L	2	3	12.4
12*	120	3	50 (6×)†	2	5	10.8
13*	105	3	50 (3×)†	2	0	10.7
14*	120	3	50 (3×)†	2	0	10.6
15*	135	3	50 (3×)†	2	5	10.9
16*	160	3	50 (3×)†	1	1	10.8
17*	120	3	50 (3×)†	2	5	10.6

* Animals 12, 13, 14, 15, 16 and 17 are designated, respectively, as 1, 2, 6, 7, 8 and 9 in table 4.
L = para-thor-mone.
† Inactivated hormone.

half that encountered in any control. In one treated animal no mitoses could be identified, and in another only a single mitosis was present. In the entire series of seventeen animals, the hormone reduced the number of mitoses to an average of 2.8 per animal. The low figures were not confined to the animals that received excessively large doses of hormone administered in a way calculated to give a maximum increase of blood calcium. In two rats (3 and 4, table 2 [12]) that received

11. Jaffe, H. L., and Bodansky, A.: J. Exper. Med. **32**:669, 1930.

12. Animals 3, 4, 5, 6, 7, 8, 9, 10 and 11 (table 2) appear, respectively, as 9, 10, 12, 13, 14, 15, 16, 17 and 18 in table 3.

a dozen doses of 10 units each, an amount insufficient to elevate the blood calcium, the gland was affected to as great an extent as in two animals (7 and 8, table 2) in which hypercalcemia was produced. In another rat (6, table 2) with high calcium, no mitosis was found. In animals 3 and 4 (table 2) an undemonstrated hypercalcemia may have been present at one time or another during the treatment. Doses of 25 units, administered on three successive days, effectively inhibited mitotic division, yet the calcium was not much increased (9, 10 and 11, table 2).

TABLE 3.—*Toxic Necroses*

Rat	Weight, Gm.	Dosage, Units and Times Injected	Duration of Experiment, Days	Blood Serum Calcium, Mg. per 100 Cc.	Necrosis of Kidney	Necrosis of Heart	Calcification of Lesions
1	104	15 (4×)	6	13.0	+	—*	+
2	118	22 (4×)	5	14.8	+	—	+
3	85	17 and 34 on alternate days	18	15.4	++	++	++
4	107	75 (1×)	1	13.6	+	—	—
5	91	50 (1×)	1	13.0	—	—	—
6	118	100 (1×)	1	12.6	+	—	—
7	86	100 (1×)	1	9.2	—	—	—
8	130	50 (4×)	7	17.0	++	++	++
9	145	10 (12×)	15	11.4	—	+	—
10	130	10 (12×)	15	10.8	—	+	—
11	142	10 (12×)	22	11.2	—	+	—
12	122	50 (3×)	10	12.1	++	+	++
13	110	50 (3×)L	3	15.1	++	+	++
14	120	50 (3×)L	3	14.4	++	+	++
15	125	50 (3×)L	3	15.5	++	—	+
16	130	25 (3×)L	3	13.6	—	+	—
17	143	25 (3×)L	3	11.2	—	—	—
18	135	25 (3×)L	3	12.4	—	—	—
19†	125	150 (1×)L	2	....	++	+	—
20†	125	150 (1×)L	2	14.8	++	+	+
21	88	18 and 36 on alternate days	16	13.7	++	—*	++

* Sections were taken across the apex where necrosis was less seen.
† See the text.

Regulatory Effect on Secretory Activity.—In young white rats, an amount of insulin insufficient to interfere with normal growth and development effectively inhibits mitotic proliferation of the pancreatic islet cells. From an examination of tables 1, 2 and 3 it appears that there is an inhibition of mitosis in the parathyroid gland by an amount of hormone that is insufficient to produce destructive lesions in the parenchymatous organs (16, 17 and 18, table 3). It is also seen in table 2 that an arrest of mitotic proliferation in the parathyroid gland is present in the absence of demonstrated hypercalcemia. After a consideration of all the data, we are inclined to view the inhibition of mitosis as the most delicate test for excessive parathyroid activity in the rat, the production of lesions in parenchymatous organs as next in this respect, and the elevation of blood calcium as the least sensitive of the three indicators.

Our results establish the efficacy of the hormone in inhibiting the normal proliferation of the parathyroid gland. That the proliferation of the various tissues is not easily inhibited by a great variety of adverse conditions is attested to by the continuous growth of the organism. We venture to advance the opinion that this hormone, as well as other hormones, by automatically acting as a regulator or governor of functional activity, exercises an effect on the cell that secretes it more delicate than the arrest of mitosis. Any excess of hormone, above the functional need, may serve to depress hormonic output, while a deficiency may stimulate output by releasing the normal activity of the cell.

The action of the inactivated hormone is of much interest. Of the three hormonic effects, parathyroid proliferation, destructive lesions and hypercalcemia, the first was the only one observed. It was decisive (table 2), although—judging from the inability to produce hypercalcemia in the dog—the inactivation was complete.

TOXICITY OF EXCESS PARATHYROID HORMONE

Collip [13] observed the lethal effect of repeated injections of the parathyroid hormone on the dog. The chief lesion noted was in the stomach, which was described as hemorrhagic and congested. An identical lesion of the stomach was produced by intravenous injection of a mixture of calcium chloride and acid sodium phosphate.[14] Hueper [15] made a histologic study of the various organs of dogs subjected to hormonic overdosage. He stated: "The effect of the hormone on the action of the heart, and the circulatory system, is the cause of the hemorrhages, thromboses, and secondary necroses in several organs." In a consideration of the lesions in the rat, the resistance of this animal to the hormonic effect should be kept in mind. Collip said: "It has been our experience that the normal rabbit and rat are immune to repeated injections of the hormone, and indeed showed very little change in the blood serum calcium values under such treatment." Tweedy and Chandler [6] were the first to offer evidence of hypercalcemia in the rat.

We first observed extensive lesions in rat 3 (table 3), which was treated on successive days with large doses of the hormone. Some of the lesions were fresh, while others were in the process of healing, so that the relations were not clear. On gross examination there were grave myocarditis, characterized by reddish, softened foci, irregular in size and shape, and large areas of necrosis in the renal cortex. It was important to determine whether these necroses were secondary to the circulatory failure, as thought by Hueper, or whether they were pri-

13. Collip, J. B.: J. Biol. Chem. **64**:485, 1925.
14. Collip, J. B.: Medicine **5**:1, 1926; Am. J. Physiol. **76**:472, 1926.
15. Hueper, W.: Arch. Path. **3**:14, 1927.

mary, and the circulatory failure secondary to the destructive lesions in the heart. This led to a study of the development of the lesions. In the rat, as in the dog, it was readily determined that preceding death the circulatory system was severely injured, with the skin surfaces becoming cyanosed and cold. In the terminal stages the tail especially showed cyanosis. Transudates were also found in the body cavities.

It is pertinent to call attention at this point to the report of Edwards and Irvine [16] on a dog given a fatal dose of hormone. Arrhythmia and a decrease in the heart rate appeared during the first twenty-four hours, but a severe fall in arterial pressure was not noted until the second twenty-four hours.

Pathogenesis of Lesions Caused by the Hormone.—A single large dose of hormone was injected into each of two rats (19 and 20, table 3). One kidney was removed for biopsy at twenty-four hours, and in it small areas of necrosis were found. At the end of forty-eight hours, necroses were present in the myocardium and in the other kidney. At this time there were neither general circulatory disturbances nor local changes, such as thromboses.

In neither these rats nor ones with larger necroses could we demonstrate thromboses of small vessels, except within the larger and older lesions, where they were secondary. In this connection, it is important to note that all animals were killed and the tissues immediately placed in the fixative. We are therefore of the opinion that the necroses are not malnutritional in origin, such as might result from general or local circulatory disturbances, but that they are toxic lesions. In these two animals and in the others of table 3, the kidneys, heart, pancreas, voluntary muscle, blood vessels, lungs, stomach, spleen, liver, suprarenal glands, thyroid gland and parathyroid glands were examined histologically. Only the first four organs named showed degenerative lesions. The skeletal system was not examined. A detailed study of the teeth is being made by Prof. Irving Schour of the Dental College of the University of Illinois, who will publish his findings in a separate report.

After the character of the twenty-four and forty-eight hour lesions caused by a single dose had been determined, the appearance of the heart and kidney after multiple injections became more intelligible. Whether the lesion calcified or not, solution of the necrotic parenchyma followed. In the heart, the solution was more rapid, and a vascularized area with a few round cells was the result. These were often perivascular in location. In the kidney, actively regenerating epithelium often was seen extending beneath the necrotic cells to form a new lining for the tubules. Injury to the myocardium and the kidney tended to run parallel, but after injection of repeated small doses (9 and 10) minute

16. Edwards, D. J., and Page, Irvine: Am. J. Physiol. **76**:207, 1926.

vascularized scars were identified in the heart only. Possibly renal lesions had been present and had healed without scar formation. The necroses observed in the pancreas (3 and 14, table 3) and the muscle (6 and 14, table 3) are discussed in a separate paragraph.

Effect of Inactivation on Toxicity of the Hormone.—In table 4 are shown the effects of the inactivated hormone on the rat and on the dog. It is seen that inhibition of parathyroid proliferation is the only one of the three hormonic effects retained after inactivation. Hypercalcemia was not found and destructive lesions of the organs were not produced.

We have considered from the first the possibility that the preparations of hormone might contain toxic substances as impurities unrelated to the hormonic component, and that these might be of such a character as to produce the lesions. If such were the case, it would be necessary

TABLE 4.—*Injections of Inactivated Hormone*

Animal	Weight, Gm.	Dosage, Units and Times Injected	Duration of Experiment, Days	Blood Serum Calcium, Mg. per 100 Cc.	Necrosis	Calcification
1	120	50 (3×)	3	10.9	—	—
2	105	50 (3×)	3	10.7	—	—
3	115	50 (3×)	3	10.3	—	—
4 (dog)	14 Kg.	140 (3×)	4	11.8*	—	—
5 (dog)	19 Kg.	140 (3×)	2	11.2*	—	—
6	120	50 (3×)	3	10.6	—	—
7	135	50 (3×)	3	10.9	—	—
8	160	50 (3×)	3	10.8	—	—
9	120	50 (3×)	3	10.6	—	—

* These are blood plasma calcium values.

to suppose that inactivation of the hormone also renders the toxic impurity inert. The absence of toxic lesions in the animals receiving inactivated hormone therefore strengthens the view that the lesions observed are caused by the parathyroid hormone and not by any associated impurity. The only determined effect of the inactivated hormone is the arrest of mitosis in the parathyroid cells (table 2). This has been discussed in the first division of the paper.

Relationship of Necrosis and Calcification.—Shelling,[17] in an extensive investigation of the effects on the rat of large doses of viosterol, observed destructive lesions of the soft tissues without calcification. He said: "Viosterol in very large doses causes a general toxic effect, since it may produce necrosis and inflammation without calcification." Viosterol then may act independently of the deposition of calcium to produce necrosis. We found this to be true for parathyroid hormone. In our hormone-treated rats we observed that necroses occurred, especially in the myocardium and kidney, without deposition of calcium

17. Shelling, D. H.: J. Biol. Chem. **96**:241, 1932.

(table 3). We were especially desirous of determining the relationship of these two pathologic changes.

Rats (19 and 20, table 3) were given injections of single doses of hormone. At the end of forty-eight hours, widespread areas of necrosis were present in the renal cortex with a very slight amount of calcium here and there. Examination of the kidneys removed by unilateral nephrectomy at twenty-four hours showed beginning necrosis without any calcium. In three rats (9, 10 and 16, table 3 [18]) there were necrotic foci in the heart without a trace of calcium. After multiple injections, early lesions without calcium and late ones with calcium may be seen in a single animal, as in rat 8, table 3.

All the observations made in the rat indicate that the necrosis occurs first, and that deposition of calcium in the degenerated areas follows.

In no animal have we seen calcification unassociated with a destructive lesion. The necrosis appears first (as early as eighteen hours, as actually determined in our experiments), and later the lesion may or may not become calcified. In rat 3(table 3), healing of the renal lesions is shown. There are long stretches of tubules entirely devoid of epithelium and consisting merely of deposits of calcium between two walls of membrana propria. Elsewhere regenerating epithelium is actively extending beneath such deposits to reline and to reform the tubules. Some of the foci finally become patches of fibrosis, while elsewhere restoration to normal results.

In the rat we have not seen metastatic calcification, in the sense that it is a deposition of lime in tissues otherwise normal. It is probable that in the hypercalcemic rats there is an increased tendency for calcium to be deposited in the necrotic tissues.

Production of Necrosis in Parenchymatous Organs by Calcium Gluconate.—Collip [14] stated that lesions could not be produced by injections of calcium salts alone. We find that by intraperitoneal injections of calcium gluconate necroses may be produced in the myocardium and kidneys of the rat (6 to 11 inclusive, table 5). Necrosis was demonstrated as early as seven hours after a series of injections, while beginning calcification of the necrotic areas was seen at eight hours. The lesions appeared to be exactly like the early hormonic ones. The rats receiving these huge doses showed severe toxic symptoms, and only two of eleven lived the eight hour period.

Local Toxic Action of Parathyroid Hormone (table 6).—Before these experiments were made, necroses seen in both the pancreas and the abdominal muscles were associated by us with local action of the hormone injected intraperitoneally. This suspicion was confirmed by

18. Animals 8, 9, 10 and 16 (table 3) are designated as 2, 3, 4 and 9, respectively, in table 2.

injection of the hormone directly into the tissues. In the kidney, a large necrotic focus was produced, not only by the hormone in the concentration used for intraperitoneal injection, but also when a 1:10 dilution of this was used. This was true for the para-thor-mone (rats 5 and 6) and also for the hormone prepared by the method of

TABLE 5.—*Injections of Calcium Gluconate*

Rat	Weight, Gm.	Dose (Cc.) of 10% Calcium Gluconate and Times Injected	Duration of Experiment	Blood Serum Calcium, Mg. per 100 Cc.	Necroses
1	145	1 (1×)	20 min.	....	.....
2	125	1 (2×)	80 min.	....	.....
3	180	1 (2×)	2 hr.	22.5*	.....
4	120	1 (4×)	6 hr.	....	.....
5	125	1 (4×)	6½ hr.	....	.....
6	135	1 (4×)	6¾ hr.	....	Kidney (minute foci)
7	140	1 (4×)	6¾ hr.	....	Kidney (minute foci)
8	140	1 (4×)	7¼ hr.	....	.....
9	150	1 (4×)	7½ hr.	....	Kidney (large foci); heart +
10	150	1 (4×)	8 hr.	22.5*	Kidney (large foci)†; heart +
11	150	1 (4×)	8 hr.	22.5*	Kidney (large foci); heart +

* Determined in a specimen of pooled serum from rats 3, 10 and 11. Difficulty was experienced in obtaining sufficient blood for analysis after the repeated injections.

† Only one, which showed distinct deposits of calcium in the form of granules. In the kidney of rat 8 deposition of calcium had begun.

TABLE 6.—*Local Action of the Hormone*

Rat	Weight, Gm.	Dosage, Units*	Duration of Experiment, Days	Tissue Into Which Injection Was Made	Necroses at Site of Injection
1	140	2 L	2	Kidney	++
2	130	2 L	2	Kidney	++
3	150	2 L	1	Kidney, spleen, internal oblique muscle	Spleen, muscle and liver
4	125	2 L	1	Kidney, spleen, internal oblique muscle	Spleen, muscle and liver
5	135	0.2 L	1	Kidney	+
6	140	0.2 L	1	Kidney	++
7	170	0.2	1	Kidney	+
8	130	0.5% cresol	1	Kidney	+
9	250	2%	1	Kidney	++
10	250	0.2	1	Kidney	++
11	220	0.2% cresol	1	Kidney	—
12	220	2% cresol	1	Kidney	+

* The dose was contained in 0.1 cc. of fluid.

Tweedy (rat 10), which contains no preservative. Acting on the assumption that para-thor-mone may contain a 0.2 per cent concentration of cresol as preservative, we injected cresol solutions of varying strengths directly into the kidney. With the higher concentration necrosis was produced, but with the more dilute solution no necrosis resulted. The necroses resulting from the direct contact of renal epithelium and hormone were the product of hormone and not of a preservative.

The Mechanism of the Toxic Action of Parathyroid Hormone.—Parathyroid hormone is not the only internal secretion known to act on the tissues to produce necrosis. Fleisher and Loeb [19] found that epinephrine is able to produce focal necroses in the myocardium of the rabbit. Later Johnson and Seibert [20] studied these destructive myocardial changes, but did not arrive at a satisfactory explanation.

Our experiments with parathyroid hormone have somewhat narrowed the problem of the manner of production of the lesions. They are not secondary to circulatory changes, either congestive heart failure or local thromboses. They are toxic lesions, which are usually associated with hypercalcemia. Since they may be produced by intraperitoneal injections of calcium gluconate, the obvious inference is that the calcium salts produce the lesions. When calcium gluconate as a 1 per cent solution was injected directly into the renal substance, no necrosis was seen about the hemorrhagic needle tract. The direct contact of calcium gluconate with parenchymal tissue appears not to produce the necrosis, but when it is injected in huge doses intraperitoneally, renal necrosis follows. The gluconate, like the parathyroid hormone and like viosterol, causes hypercalcemia. The hypercalcemia is likely associated with a disturbance in the relationship of ionized, nonionized, bound and unbound calcium both in the blood plasma and in the tissue lymph that bathes parenchymal cells. In the latter location, the changed calcium composition of the fluid so injures the cell that necrosis follows. The hormone when injected directly into the renal substances has a similar action.

CONCLUSIONS

Parathyroid hormone inhibits mitotic proliferation of the parathyroid gland. It does this in amounts insufficient to produce hypercalcemia and destructive lesions of parenchymatous organs.

The lesions produced by excessive doses of the hormone are toxic and primary. The circulatory failure which characterizes the fatal cases is secondary to the destructive lesions in the myocardium.

The hormone when brought into direct contact with parenchymatous cells produces lesions analogous to those produced after its absorption into the blood stream. Necroses are produced in the kidney and heart by intraperitoneal injection of calcium gluconate alone. It is probable that the hormone and calcium gluconate as well as viosterol injure parenchymal cells by disturbing the calcium components of the tissue fluids of the cells themselves.

There is no evidence of metastatic calcification in the rat in the sense that the calcium is deposited in tissue otherwise normal. In the

19. Fleisher, M. S., and Loeb, L.: Arch. Int. Med. **3**:78, 1909.
20. Johnson, S., and Seibert, W. J.: Am. Heart J. **3**:279, 1928.

rat, local degenerations of the tissues are primary and precede calcification.

Amounts of hormone insufficient to produce effects demonstrable by the methods previously used successfully arrest mitotic proliferation of the parathyroid gland. Amounts not large enough to elevate the serum calcium may cause myocardial lesions.

Inactivated hormone, completely inert as determined by the usual method employed for testing activity, arrests parathyroid proliferation, but produces neither hypercalcemia nor destructive lesions.

TRANSFUSION EXPERIMENTS WITH THE BLOOD OF LEUKEMIC CHICKENS

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AND

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PHILADELPHIA

Studies of avian tumors caused by filtrable agents have shown that the tumor cells produced by these agents behave like neoplastic cells (Rous [1]). Attention has been called to the similarity between avian sarcoma and avian leukosis.[2] This view is much strengthened by recent investigations [3] showing that avian leukosis, like avian sarcoma and unlike leukemia and tumors of mammals, may be transmitted by a cell-free agent, which passes bacteria-tight filters, resists freezing and thawing, and drying, and can be preserved by the addition of glycerin. However, direct evidence for the neoplastic character of the leukemic cells has hitherto been wanting. The differences in behavior between cell-free filtrate and cell-containing material transmitting leukosis might be explained by assuming that they are due to the position of the agent, largely intracellular in one instance, free in the other. Whether this agent is an ordinary virus or not, leukosis may be conceived of either as hyperplasia or as neoplasia of the myeloid and erythroblastic elements of the bone marrow.

Should the view be correct that leukosis is a neoplastic process caused by an ordinary virus, the immature blood cell may be expected to multiply and to retain transmissibility even after the disappearance of the causative agent. A similar phenomenon has been observed with mammalian tumors caused by infective agents.[4] Avian tumors caused by filtrable agents are, however, not known to be changeable into tumors that are transmissible only by material containing cells. Yet this

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1. Rous, P.: J. Exper. Med. **18**:416, 1913.

2. Opie, E. L.: Medicine **7**:31, 1928.

3. Furth, J.: J. Exper. Med. **55**:465, 1932.

4. Fibiger, J.: Overs. o. d. kong. Danske Videnskabernas Selsk. Forh., 1913, no. 1, p. 47. Jensen, C. O.: Den kongelige Veterinaer-og Landbohøjskoles Aarsskrift, Copenhagen, 1918, p. 91. Both references are quoted from Krebs, C.; Rask-Nielsen, H. C., and Wagner, A.: Acta radiol., supp. 10, 1930, p. 1.

would frequently occur were these agents viruses characterized by the capacity to produce strong immunity in the animals affected. A fowl immune to the filtrable agent of leukosis was inoculated with leukemic cells.[5] We looked for an inactivation of the agent and a transformation of avian leukosis transmissible by a filtrable agent into avian leukosis transmissible only by leukemic cells. This supposition was not substantiated; the cell-free plasma of a fowl thus treated readily transmitted the disease.[5]

The experiments to be described were made in an attempt to ascertain whether leukemic cells introduced into the circulation in large numbers are capable of autonomous growth in the body of a susceptible host.

Minot and Isaacs [6] transfused blood of a patient with lymphatic leukemia into one with aleukemic lymphoma and noted almost complete removal of the immature lymphocytes from the circulation within thirty minutes. Experiments with transmissible lymphoid leukemia of mice [7] indicate that leukemic lymphocytes introduced into the circulation of healthy mice lodge and multiply mainly in the lymphoid tissues and secondarily invade the circulating blood. Lymphocytes from mice with malignant aleukemic lymphadenosis,[8] when injected into the veins of healthy mice, likewise multiply in lymphoid tissues and infiltrate many organs, but do not invade the blood stream to any considerable extent.

Leukosis of fowls differs from lymphoid leukemia of guinea-pigs and mice [9] in that it is transmissible by a cell-free filtrable agent. Since mammalian lymphoid leukemia may be reproducible by cells, it is again pertinent to inquire whether avian leukosis may result from the multiplication of transfused leukemic cells.

FIRST SERIES OF TRANSFUSION EXPERIMENTS

From 15 to 35 cc. of the blood of fowls with severe myeloid leukemia was transfused into each of seven young chickens after a like or somewhat smaller amount of blood had been removed from the circulation of the recipient. In five of these fowls the transfused immature myeloid cells were rapidly removed from the circulation, but in two of them they multiplied rapidly, causing death within three days with the blood picture of leukemia. Figure 1 *A* and *B*, table 1 and the history of four fowls illustrate these observations.

5. Furth, J.: Immunity Phenomena in Transmissible Leucosis of Fowls, Proc. Soc. Exper. Biol. & Med. **29**:1236, 1932.

6. Minot, G. R., and Isaacs, R.: J. A. M. A. **84**:1713, 1925.

7. Furth, J., and Strumia, M.: J. Exper. Med. **53**:715, 1931.

8. Seibold, H. R.; Rathbone, R. R., and Furth, J.: Proc. Soc. Exper. Biol. & Med. **29**:629, 1932.

9. Tio Tjwan Gie: Over leukaemie bij dieren, Amsterdam, 1927. Korteweg, R.: Ztschr. f. Krebsforsch. **29**:455, 1929. MacDowell, E. C., and Richter, M. N.: Science **74**:605, 1931.

Notes to Table 1.—The column headed "Primitive Myeloid Cells" refers to the cells illustrated in figure 1*A*; the majority of these are primitive mononuclear cells, or myeloblasts according to Ellermann. Many similar cells contained lobed nuclei or several nuclei; these, called poikilonuclear cells by Ellermann and Rieder cells by others, are included in this column. A few such cells containing purple granules (promyelocytes) were also counted with these. The myeloid cells of this fowl will be more fully described in a later report. The column headed "Polychrome Red Cells" includes both polychrome erythroblasts and erythrocytes. The percentage of normal leukocytes decreased following the transfusion, but their absolute number increased somewhat. The bulk of the increase in white cells is referable to an increase in primitive large mononuclear leukocytes.

TABLE 1.—*Blood Changes in Fowls That Had Received a Transfusion of Leukemic Blood*

Fowl	Time of Examination with Relation to Transfusion	Hemoglobin, (Sahli), per Cent	Red Cell Count, Thousands	White Cell Count, Thousands	Polychrome Red Cells, Thousands	Basophil Erythroblasts, Thousands	Polymorphonuclear Leukocytes, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Mast Cells, per Cent	Primitive Myeloid Cells, per Cent
1627	Before.....	46	2,530	30	3	0	18	69	6	6	1
	30 min. after...	41	1,570	189	54	4	2	14	1	1	82
	1 day after....	34	1,870	265	21	0	2	5	1	1	91
	2 days after...	32	1,405	265	29	0	2	6	1	1	90
	3 days after...	38	1,645	585	29	0	2	6	0.5	0.5	91
1493	Before.....	59	2,355	27.5	0	0	30	60	4	6	0
	30 min. after...	35	1,560	365	58	4	7	11	0.5	0.5	81
	3 days after...	27	1,240	910	15	0	1.5	1.5	0.5	0	92.5
	(In vitro mixture of donor's and recipient's blood [1:3])	36	1,875	912	110	10	4.5	3.5	0.5	0.5	91
1106	Before.....	56	2,890	48.5	0	0	32	61	6	1	0
	30 min. after...	37	1,500	173	107	20	21	11	4	1	62
	1 day after....	34	1,585	153	29	2	22	20	2	2	54
	2 days after...	34	1,505	230	27	0	20.5	15	3	0.5	61
	4 days after...	32	1,305	107	51	2	22	40	1	3	34
	6 days after...	39	1,710	91	0	0	30	59	9	1	0
	8 days after...	34	1,735	81	0	0	15	68	5	2	0
	11 days after...	53	2,500	48	0	0	18	76	5	1	0
	14 days after...	55	3,000	43	0	0	29	64	5	2	0

Experiment 1.—Thirty cubic centimeters of blood of a fowl with severe myeloid leukemia was transfused into a chicken weighing 870 Gm. The white cell count of the donor was 975,000; the red cell count, 1,030,000, and the hemoglobin content, 18 per cent (Sahli). The blood counts of the recipient before and after the transfusion are recorded in table 1. (See also figure 1*A*.) There was a rapid, progressive rise of the immature myeloid cells in the circulation, causing death of the fowl three days after the transfusion. In blood smears taken before death, large numbers of mitotic figures were seen (fig. 2*A*). At postmortem examination, the liver and the spleen were somewhat enlarged; their pale grayish color suggested an invasion by white cells. Microscopically, stasis of immature myeloid cells was observed in many organs, notably in the lung (fig. 2*C*), spleen (fig. 3*E*), liver (fig. 3*A*), kidney (fig. 2*E*) and adrenal gland. In the liver there

were, also, numerous large tumor-like foci formed apparently by multiplying myeloid cells. Most of the bone marrow was composed of fat (fig. 2 *B*); only a few small areas were seen that showed the character of leukotic growth, namely, multiplication of primitive cells with little or no maturation.

Experiment 2.—Twenty cubic centimeters of leukemic blood was transfused into a fowl weighing 750 Gm., after the removal of 15 cc. of its own blood. The leukemic blood had a white cell count of 915,000, a red cell count of 540,000 and a hemoglobin content of 14 per cent (Sahli). As in the preceding fowl, the transfusion was followed by a progressive rise in the number of circulating immature myeloid cells (table 1), terminating in death three days after the transfusion. The gross and microscopic appearances of the organs of this fowl were essentially the same as those described in experiment 1.

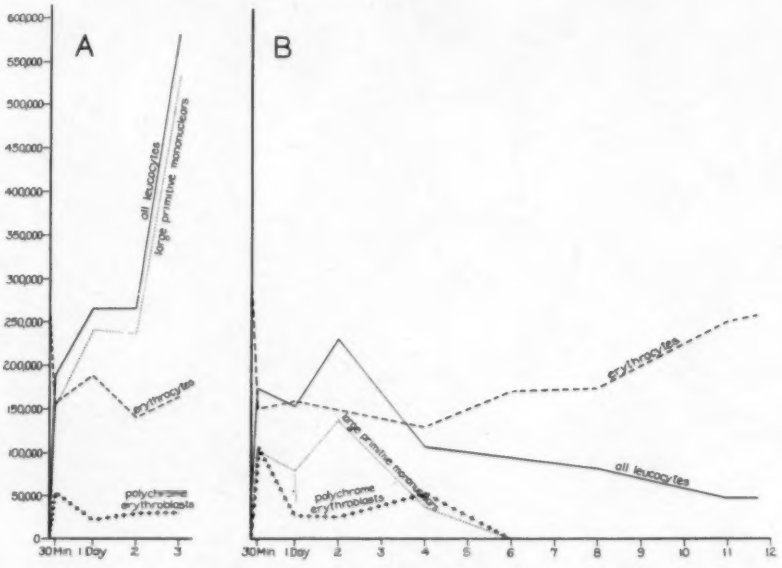

Fig. 1.—*A*, chart showing the changes in the number of blood cells of a fowl after it had received a transfusion of 30 cc. of leukemic blood. The fowl died of leukemia three days after the transfusion. *B*, chart showing the changes in the number of blood cells of a fowl that had received a transfusion of 30 cc. of leukemic blood. The transfused cells rapidly disappeared from the circulation.

In these two experiments, massive transfusion of leukemic blood into two healthy fowls resulted in leukemia fatal on the third day after the transfusion. The effect of the transfusion on the number of circulating leukocytes is shown in table 2. The figures in table 2 do not give exact information as to the rate of multiplication of the transfused primitive myeloid cells, mainly because these cells are retained in large numbers in the capillaries of many organs, and data on the number of immature leukocytes thus removed from the circulation and on the rate of their multiplication in the capillary bed are wanting. However, large numbers of mitotic figures seen in the circulating blood as well as in the

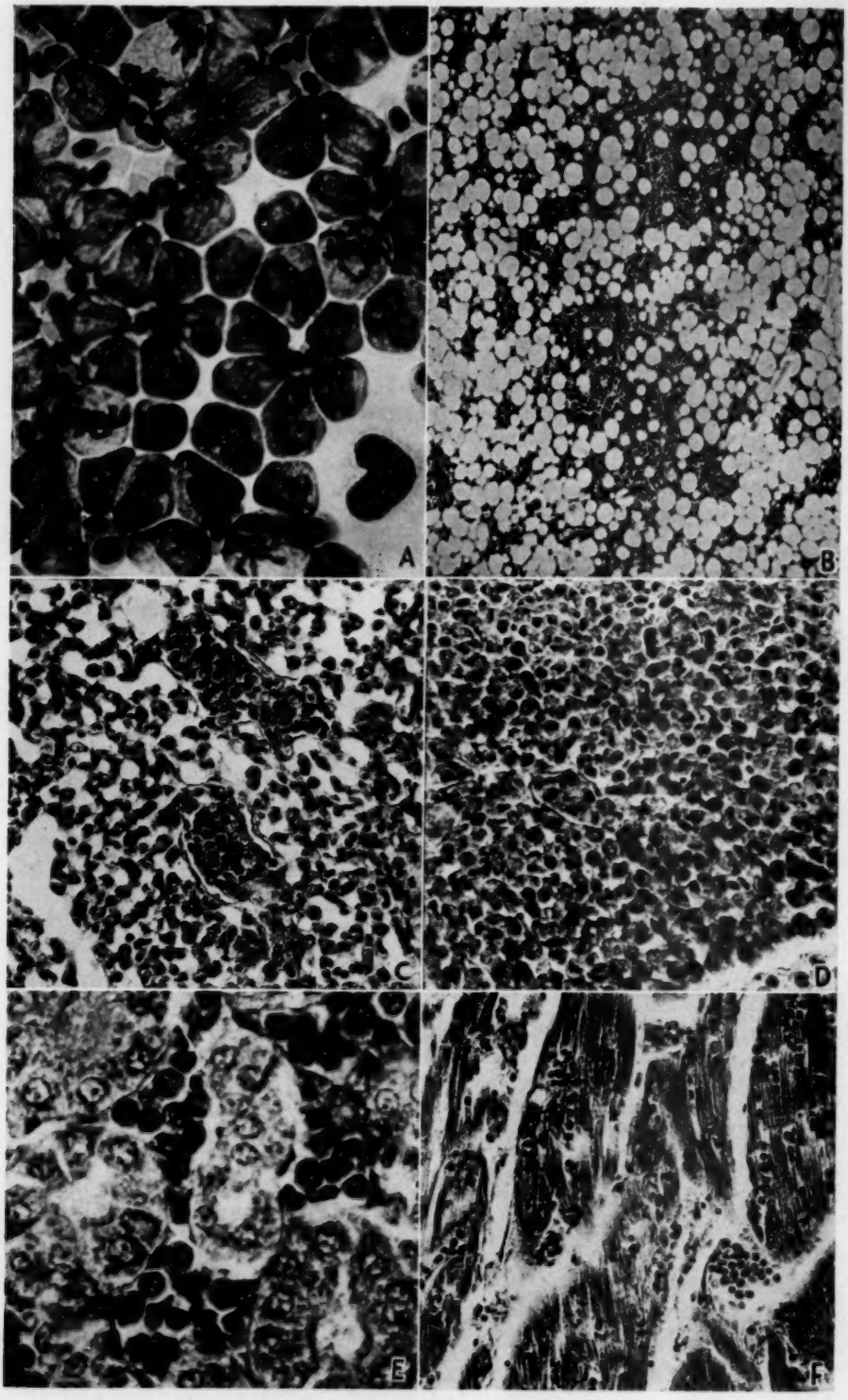

FIGURE 2

Photomicrographs are shown of material from fowls that died about three days after receiving a transfusion of leukemic blood. The blood smear is stained with Wright and Kiemsa's solution, and the slides, with hematoxylin and eosin. The magnifications given are only approximate. *A* shows a blood smear with four mitotic figures in a field (× 900); *B*, femoral marrow containing abundant fat (× 25); *C*, capillaries of the lung distended with myeloid cells (× 250; *D*, an atelectatic area of the lung, its capillaries filled with myeloid cells, many of them in mitotic division (× 300); *E*, mild stasis of myeloid cells in the kidney (× 500), and *F*, mild stasis of myeloid cells in the heart muscle (× 200).

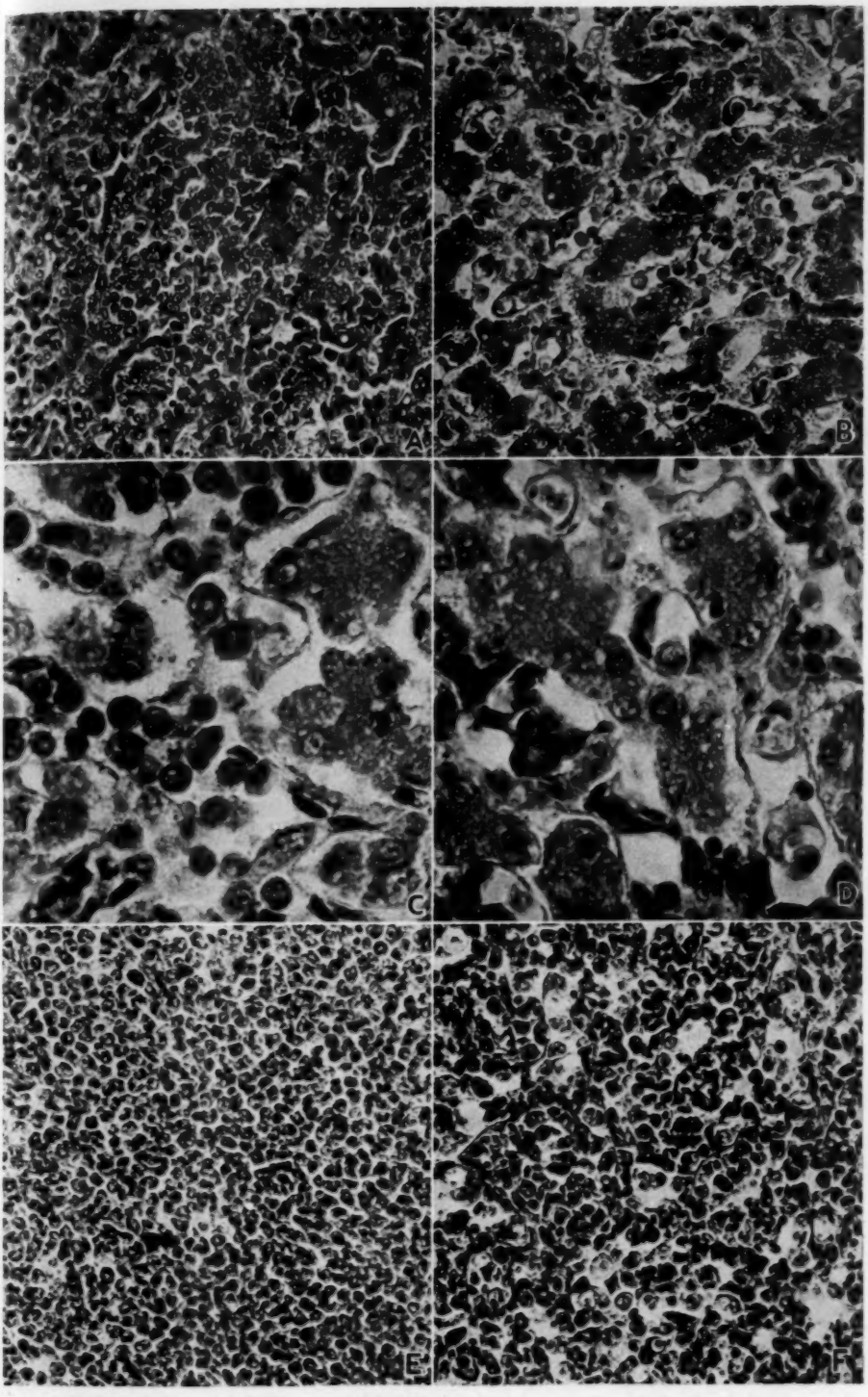

FIGURE 3

Photomicrographs of liver and spleen of fowls dying with leukemia about three days after they had received a transfusion of leukemic blood are contrasted with those of fowls in which there was a rapid removal of the transfused leukemic cells. The slides were stained with hematoxylin and eosin. The magnifications given are only approximate. *A* shows liver from a fowl dying with leukemia after transfusion (× 250). Note the accumulation of large numbers of apparently viable cells in the capillaries, showing practically no tendency of the host to remove them. *B* shows liver from a fowl in which the transfused leukemic cells disappeared from the circulation (× 250). Intact leukemic cells are scant in the capillaries, while the Kupffer cells show extensive phagocytic activity. *C* is a higher magnification (× 600) of the slide shown in *A*, and *D*, a higher magnification (× 600) of the slide shown in *B*. *E* pictures the spleen of a fowl dying with leukemia after transfusion (× 250). The pulp is densely crowded with apparently viable leukemic cells; little, if any, phagocytic activity is seen. *F* shows the spleen of a fowl in which the transfused leukemic cells disappeared from the circulation (× 250). Mononuclear phagocytes engulfing cells or cellular débris are abundant in the field.

capillaries may be taken as an indication that the transfused cells underwent rapid multiplication (fig. 2 *A* and *D*). It is hardly conceivable that the normal marrow of a fowl would be capable of producing leukocytes in such numbers in such a short time. Moreover, this possibility is excluded by an examination of the marrow after death, which showed abundant fat and little new formation of myeloid cells (fig. 2 *B*). Growth within blood vessels, an abnormal site for myeloblast formation, had taken place apparently throughout the vascular bed; extravascular growth, localized mainly in the liver and the bone marrow, was relatively slight.

Experiment 3 is described as an example of five experiments in which transfusion of leukemic blood was followed within a few days by complete disappearance of the immature blood cells from the recipient's circulation. Three of the five fowls showed no further change, but in one erythroleukosis developed forty-seven days after the transfusion.

TABLE 2.—*Effect of a Transfusion of Leukemic Blood on the Leukocyte Counts of Healthy Fowls*

Fowl	Count Before Transfusion	30 Minutes After Transfusion	3 Days After Transfusion
1623	30,000	189,000	585,000
1493	27,500	365,000	910,000

Experiment 3.—Thirty-five cubic centimeters of leukemic blood was transfused into a fowl after the removal of 30 cc. of its blood. The white cell count of the leukemic blood was 1,050,000; the red cell count, 750,000, and the hemoglobin content, 19 per cent (Sahli). The blood counts and differential counts of the recipient made before and after the transfusion are recorded in table 1. (See also figure 1 *B*.) The highest number of immature blood cells in the circulation was observed two days after the transfusion (white cell count, 230,000); four days after the transfusion, their number had decreased considerably, and two days later there was merely a leukocytosis due to an increase of normal lymphocytes, polymorphonuclear leukocytes and monocytes. Subsequent examinations of the blood during a period of five months and the postmortem examination showed neither anemia nor leukemia.

As another example of the rapid elimination of immature leukocytes from the circulation of healthy fowls, a fowl may be cited the white cell count of which was 17,000 before transfusion, 218,000 one-half hour after transfusion and 34,500 three days after transfusion.

SECOND SERIES OF TRANSFUSION EXPERIMENTS

About a year after the experiments reported in the foregoing paragraphs had been completed, eight chickens, weighing from 550 to 750 Gm., were given transfusions of leukemic blood in the manner described. These experiments were undertaken to throw light on the mode of removal of the transfused cells. It is remarkable that in the

case of only one of the eight chickens was there a drop in the high leukocyte count caused by the mechanical effect of transfusion; the rest died with the blood picture of leukemia from two to three and a half days after the transfusion.

The view that the rise in the blood counts of these seven fowls following the transfusion (table 3) indicates multiplication of these cells in the recipients was strengthened by the observation of numerous mitotic figures in smears as well as by that of the absence of conspicuous myeloid hyperplasia of the marrow. Nevertheless, it is evident from the figures given in table 3 that the death of the fowls from two to three and

TABLE 3.—*Transfusion Experiments (Second Series)*

					Recipient's Blood Count, Thousands						
	Volume of Blood, Cc.		Donor's Blood Count, Thousands		Before Transfusion		½ to 1½ Hr. After Transfusion		2 Days After Transfusion		
Recipient	Removed	Injected	White Blood Cells	Red Blood Cells	White Blood Cells	Red Blood Cells	White Blood Cells	Red Blood Cells	White Blood Cells	Red Blood Cells	Comment
2332	20	40	995	1,150	16.7	1,822	405	1,310	850	1,095	Died 2½ days after transfusion
2330	15	25	1,120	895	35	1,950	420	1,395	740	1,025	Died 3½ days after transfusion
2333	17	25	1,120	895	29.5	2,430	645	1,540	1,390	1,150	Died 2 days after transfusion
2346	8	10	1,390	1,150	43	2,650	208	2,185	400	1,410	Died 2½ days after transfusion
2347	10	10	1,390	1,150	39.5	2,820	120	2,455	204	1,500	Died 2 days after transfusion
									3 Days After		
2348	10	20	690	1,180	31.5	2,005	119	1,820	182	1,720	Died 3 days after transfusion
2349	10	20	690	1,180	19	2,920	74	1,870	153	1,485	Died 3½ days after transfusion
2327	20	30	405	1,412	45	2,505	230	1,745	81.5	1,330	Active; killed 3 days after transfusion

a half days after the transfusion cannot be correlated with the height of their white cell counts. These counts from two to three days after the transfusion were about double those obtained from one-half to one and a half hours after the transfusion, whether increasing from 74,000 to 153,000 or from 645,000 to 1,390,000. What characterizes this group is not the height of the white cell counts, but their conspicuous rise in two and three days after the transfusion. On the other hand, fowls in which there was a drop in the number of white cells three days after the transfusion (fowl *2327* of series *2* and five fowls of series 1) appeared active, and if permitted to live, recovered from the immediate effects of the transfusion.

It is a matter of conjecture why most of the fowls of the first series resisted the transfusion, whereas most of the fowls of the second series succumbed to it. Increased virulence of the leukemic cells, selection of

somewhat younger birds or improved technic may be responsible for this difference.

COMMENT ON THE TRANSFUSION EXPERIMENTS

When large amounts of leukemic blood are transfused into fowls, either the white cells introduced into the circulation continue to increase in number within the vascular bed and the fowls die with the blood picture of leukemia from two to four days after the transfusion, or most of the transfused cells disappear from the circulation within three days, and the blood picture gradually returns to normal. Resistance and susceptibility in these instances are explained with most probability by an assumption of genetic differences similar to those that govern the fate of tumor grafts.

The experiments described indicate that leukemic chicken cells introduced into susceptible hosts are capable of autonomous growth. The behavior of lymphocytes causing lymphoid leukosis of mice [10] suggested a similar conclusion. Accordingly, it may be supposed that leukemic cells from either animal would multiply in vitro under favorable conditions as do cancer cells. Contrary to these suggestions, investigators studying the behavior of leukemic cells of man in tissue cultures describe, instead of multiplication, maturation.

ANATOMIC CHANGES IN FOWLS THAT RECEIVED TRANSFUSIONS OF LEUKEMIC BLOOD

In order to determine the site of retention and subsequent disposal of the introduced cells in resistant fowls, seven such chickens that had received transfusions of leukemic blood were killed at different intervals after the transfusion, and their organs examined microscopically.

There are numerous studies on the mechanism of the disposal of foreign particles introduced into the circulation as well as of cell débris originating within the body. For a review of the literature see Drinker and Shaw.[11]

Two fowls were studied one and a half hours after they had received the transfusion of leukemic blood. The white cell count rose in one to 350,000, as a result of the transfusion, and in the other, to 245,000. One fowl, examined twenty-four hours after it had received the transfusion of leukemic blood, had a white cell count of 260,000 one and a half hours after the transfusion and one of 220,000 before death. Two fowls were examined three days after they had received the transfusion. The white cell count was 218,000 one-half hour after the transfusion and 34,500 before death, in one, and in the other, 230,000 and 81,500, respectively. In both fowls the blood smears taken before death showed many primitive mononuclear cells (myeloblasts). Two other fowls that died of leukemia three days after they had received a transfusion of leukemic blood have been described (pp. 662 and 663). Two fowls were studied six days after they had received a transfusion, one

10. Furth and Strumia.[7] Seibold, Rathbone and Furth.[8]

11. Drinker, C. K., and Shaw, L. A.: J. Exper. Med. **33**:77, 1921.

of 12 and the other of 25 cc. of leukemic blood. In smears taken before death there were practically no immature myeloid cells, but a few erythroblasts had made their appearance, suggesting the onset of erythroleukosis caused by the transfused leukemic material.

It is evident from the microscopic appearance of the organs of these fowls that a considerable proportion of transfused leukemic cells was retained in the pulp of the spleen and in the capillaries of several organs, notably the lung and the liver. The part played by the spleen was especially prominent; the pulp appeared to be filled to capacity thirty minutes after the transfusion and thereafter for about six days. The behavior of the bone marrow was very different; here sinusoidal capillaries were filled with erythrocytes, but among them only a few primitive myeloid cells of the type transfused were seen.

In the fowl examined twenty-four hours after transfusion there was phagocytosis of cellular débris by the Kupffer cells, but the majority of the primitive myeloid cells filling the pulp of the spleen and accumulating in the capillaries of the liver appeared viable. Myeloid cells were much more numerous in the sinusoidal capillaries of the bone marrow in this fowl than in those examined one-half hour after the transfusion, and many so-called intersinusoidal capillaries contained such cells almost exclusively.

In the fowls examined three days after transfusion, the appearance of the larger blood vessels indicated that most of the immature white cells had been removed from the circulation. Stasis of myeloid cells in the pulp of the spleen and in the capillaries of the liver and of the lung was less extensive than in the fowl just described; phagocytosis by mononuclear leukocytes, on the other hand, was more conspicuous (fig. 3 *B*, *D* and *F*). In the bone marrow, primitive mononuclear cells were abundant; among them were numerous myelocytes. Most of the erythrogenic capillaries were collapsed. Their lining could not be clearly distinguished, and for this reason it could not be determined with certainty whether this accumulation of myeloid cells had occurred only in extravascular tissues. It likewise remains a matter of conjecture whether the increase in the number of primitive nongranular myeloid cells was due to a slow migration of transfused myeloid cells to the marrow, or to a myeloid hyperplasia of the marrow, or to both.

In the fowls examined six days after the transfusion the Kupffer cells showed phagocytosis. The splenic pulp was filled with cells showing karyorrhexis and pyknosis, but here phagocytosis by mononuclear leukocytes was less pronounced, suggesting that lysis may be one of the means of disposal of dead cells.[12] The bone marrow showed mild nonspecific hyperplasia of all its elements.

12. Strauss, A.: Beitr. z. path. Anat. u. z. allg. Path. **85**:251, 1930.

COMPARISON OF ANATOMIC CHANGES IN SUSCEPTIBLE AND RESISTANT FOWLS THAT RECEIVED TRANSFUSIONS OF LEUKEMIC BLOOD

In a comparison of the microscopic appearances of the organs of susceptible and resistant fowls three days after the transfusion of leukemic blood, the differences in their reaction to the foreign leukemic cells are clearly seen. In susceptible fowls, the capillaries of the lung are filled with leukocytes, causing in some areas almost complete atelectasis. The pulp of the spleen, too, is filled with leukocytes, and there are numerous mitotic figures among these cells in both the lung and the spleen. In the capillaries of several other organs, e. g., the liver, there is slight to moderate stasis of the leukemic cells. In resistant fowls, on the other hand, there are relatively few leukemic cells in the capillaries of these organs, and large mononuclear phagocytes containing cells or cellular débris are abundant in the liver and spleen. There is slight, if any, phagocytosis in the lung, suggesting that the cells retained in the pulmonary capillaries immediately after transfusion may be subsequently released and disposed of in the spleen and liver as described by Drinker and Shaw.[11]

SUMMARY AND CONCLUSIONS

Of fifteen fowls into which leukemic blood had been transfused, nine died of leukemia from two to three and one-half days after the transfusion. The fatal leukemia in these instances was associated with multiplication of the transfused cells. Thus, when immature myeloid cells of the fowl have been stimulated by the filtrable agent of leukosis, they assume the character of tumor cells and are capable of autonomous growth.

A considerable proportion of the transfused cells was rapidly removed from the circulation in all the fowls. The spleen and the capillaries of several organs, mainly those of the liver and the lung, are active in performing this function. The bone marrow plays little part in the removal of the immature myeloid cells. In susceptible fowls, the cells retained multiply in these sites; in resistant fowls, they are disposed of by mononuclear phagocytes of the liver and spleen.

TRUNCUS ARTERIOSUS COMMUNIS PERSISTENS

CRITERIA FOR IDENTIFICATION OF THE COMMON ARTERIAL TRUNK, WITH REPORT OF A CASE WITH FOUR SEMILUNAR CUSPS

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CHICAGO

Among the rare congenital defects of the heart is persistence of the primitive common arterial trunk. This is one of the most interesting of anomalies from a developmental point of view, as it involves a failure of certain of the primary septums, those of the arterial trunk and cardiac bulb. Hence it dates from a very early stage of cardiac development. Many of the cases reported under this heading are really examples of other defects. In spite of the increased appreciation of the embryologic basis of the anomaly, opinion varies widely as to which cases should be included in this group. Herxheimer [1] accepted forty-three cases. Abbott [2] recognized twenty-three cases, fourteen of which she analyzed and classed as instances of the "complete" defect. Recent critical reviews in the German literature have rejected many of these examples. Shapiro [3] recently stated that he knew of but two cases that fulfilled all requirements for identification of the defect.

Because of the confusion that prevails, it seems advisable to review the criteria for identification of the anomaly in the light of the newer embryologic knowledge. These criteria will be applied to an example of partial (almost complete) persistence of the common arterial trunk, one of the five reported cases in which four semilunar cusps have been found.

EMBRYOLOGIC AND ANATOMIC FACTORS

Detailed reviews of the embryologic development of the heart are available in the works of Tandler,[4] Abbott,[5] Mönckeberg [6] and others.

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From the Department of Pathology, University of Chicago.

1. Herxheimer, Gotthold: Missbildungen des Herzens und der Grossen Gefässe, in Schwalbe: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1910, pt. 3, no. 3, sect. 2, p. 427.

2. Abbott, M. E.: Congenital Cardiac Disease, in Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1927, p. 612.

3. Shapiro, P. F.: Arch. Path. **10**:671, 1930.

4. Tandler, Julius: Anatomie des Herzens, in Bardelben: Handbuch der Anatomie des Menschen, Jena, Gustav Fischer, 1913, vol. 3, pt. 1, p. 1.

5. Abbott, M. E., and Shanley, Eleanor: Internat. A. M. Museums Bull. **8**: 188, 1922. Abbott.[2]

6. Mönckeberg, J. G.: Die Missbildungen des Herzens, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 1.

Only those features of special interest for the interpretation of the anomaly under consideration will be considered here.

The normal division of the primitive tubular arterial trunk and cardiac bulb occurs in the early weeks of development. Three elements aid in the division. These are the two proximal swellings of the bulb, which assist in forming the interventricular septum; the four distal swellings of the bulb, which form the distal bulb septum, and from the lower ends of which the semilunar cusps are derived, and the aortic-pulmonary septum, which completes the divison of the trunk. Thus in an early stage of development the systemic and pulmonic blood streams are separated, except for the communications through the foramen ovale and ductus arteriosus, which normally become closed only after birth.

Aortic-Pulmonary Septum.—It is generally held that the aortic-pulmonary septum is first demarcated distally by the spurs between the fourth and sixth pairs of aortic arches. The left member of the fourth pair is destined to form the arch of the aorta and its branches, except the right subclavian artery, which develops from the right fourth arch. From the sixth pair come the right and left pulmonary arteries, and from the left, the ductus arteriosus. Fusion of the paired spurs and caudal extension of the resulting septum divide the primitive trunk into the aorta and the pulmonary artery. The septum bisects and grows through the larger opposed (lateral) pair of distal swellings, which fuse near their midpoints. Thus three swellings are contributed to each arterial ostium, as the anlagen for the semilunar cusps. The caudal end of the septum then joins with the proximal bulb septum to complete the separation of the two arterial conuses and of the ventricles in which they become incorporated.

Accounts differ as to the manner of development of this septum. Mönckeberg,[6] following Born and Broman, held that it develops from two longitudinal ridges, or swellings, which come to separate the two blood streams by fusion of their margins and by caudal extension. Tandler's[4] view, supported by Wirtinger's[7] observations, is that the septum proceeds caudally as an arched membrane, sending ahead longitudinal ridges as forerunners of its course. Spitzer's[8] theory is that fusion of the two spurs and proximal migration are due to two factors. The increased flow of blood, due to opening of the pulmonary capillary bed, leads to a widening and shortening of the primitive trunk, causing a relative descent. The increasing blood pressure on the two surfaces of the septum causes a further centripetal migration, in which the forerun-

7. Wirtinger, cited by Feller, A.: Virchows Arch. f. path. Anat. **279**:869, 1931.

8. Spitzer, Alexander: Virchows Arch. f. path. Anat. **243**:81, 1923.

ners descend ahead of the arched septum. On histologic grounds, Tandler [4] believed that the aortic-pulmonary septum grows through the line of fusion of the distal bulb swellings, thus forming the septum of the extracardiac portion of the bulb, as well as of the trunk.

Septum of the Proximal (Cardiac) Bulb.—The complex upper part of the interventricular septum is formed by a fusion of the primitive ventricular septum with the two proximal swellings of the bulb and with the anterior endocardial cushion of the atrioventricular ostium (Tandler [4]). It is difficult to identify the different elements in the definitive state. Spitzer [8] concluded from a study of the model of the heart of a 14.5 mm. human embryo, prepared by Tandler, that the course of the muscle structures constituting the crista aorticopulmonalis and the anterior tricuspid ledge indicates derivation from the bulb swellings and the anterior endocardial cushion. The relations of these structures to the distal bulb swellings of the base of the arterial trunk and to the anterior tricuspid leaflet indicate an intimate fusion rather than a juxtaposition of the elements derived from the bulb and the cushion.

The point of closure of the interventricular septum is in the anterior part of the membranous septum. A simple interventricular foramen associated with a failure of union of the elements named is located immediately beneath the aortic ostium, which is frequently shifted to the right, in the position of the "rider" aorta. With defects involving only the posterior part of the anterior septum (Rokitansky), the opening stands above a Y-shaped muscle ledge on the right wall of the septum. This is part of the crista and ledge referred to in the foregoing paragraph, and will be described later. The opening is bordered anteriorly by the remnant of the anterior swelling and a forerunner of the primitive ventricular septum; posteriorly, by the rest of the membranous septum from the anterior endocardial cushion, and behind that, by the posterior muscular septum from the cushion and the posterior forerunner of the interventricular septum. Its lower margin, between the divergent limbs of the Y, is formed by fused remnants of the anterior swelling, the posterior swelling and a protuberance of the right anterior endocardial cushion. Except with more extreme septal defects, the primitive interventricular septum does not border the opening.

Semilunar Cusps and Coronary Arteries.—For an analysis of cardiac defects a study of the relationships of the semilunar cusps to adjacent structures and to the coronary arteries is essential. If normally placed, the coronary ostia identify the cusps. In identifying and naming the coronaries, however, one must take into consideration the type of the cardiac defect. Spitzer [8] has shown that with extreme detorsion one

coronary stem may take over or "adopt" many of the branches normally derived from the other. Thus, the apparent left coronary may be the right and vice versa. Even in otherwise normal hearts, variations of origin and course are common. Minor shifts of the ostia are frequent. Occasionally one ostium is shifted above the commissure between its cusp and that of the other coronary, so that the two may appear to arise from one sinus. Less frequently only one coronary stem may be present and may send branches to the field normally supplied by the other. With absence of the main stem, two ostia may be present in a single sinus. A rarer anomaly is the presence of only one aortic coronary, the other, usually the left, originating from a sinus of the pulmonary artery. With such variability, it is obvious why the coronary arteries identify the cusps only when found in the expected positions.

Little is known of the early development of the coronary arteries. From their studies of rabbit embryos, Martin [9] and Lewis [10] both concluded that the anlagen are recognizable before the division of the bulb. From their normal relationships it is obvious that they develop in relation to the larger (lateral) pair of distal bulb swellings. Obviously, too, their sites should be shifted toward the junctions of these swellings with the swelling for the future noncoronary aortic cusp. Thus, before rotation, the left coronary should originate near the anterior half of the right swelling, and the right, from the corresponding part of the left swelling, opposite. Normal torsion of 180 degrees would bring swellings and coronaries into their final normal relationships. After fusion and bisection of the lateral swellings, the anterior (pulmonic) ostium has three cusps, anterior and left and right posterior; the posterior (aortic ostium has the same number, posterior (noncoronary) and left and right anterior. If normally placed, the left coronary rises behind the left anterior, the right behind the right anterior, aortic cusp.

On theoretical grounds one would demand four semilunar cusps for the positive identification of a persistent common trunk. Gierke,[11] Wirth,[12] Pietzch [13] and Hülse [14] have emphasized this point, while admitting that anomalies of number of swellings may occur as a primary anomaly. Simonds [15] found 209 recorded cases of alteration in number of semilunar cusps, forty-three in 15,666 autopsies. Many of these were

9. Martin, Henri: Compt. rend. Soc. de biol. **6**:83, 1894.

10. Lewis, F. T.: Anat. Anz. **25**:261, 1904.

11. Gierke, Edgar: Charité-Ann. **32**:299, 1908.

12. Wirth, A.: Ein Fall von totaler Persistenz des Truncus arteriosus communis, Diss., Giessen, 1912; cited by Mönckeberg.[6]

13. Pietzch, Johannes: Ueber zwei Fälle von Atresia ostii aortae congenita, Diss., Freiburg; cited by Mönckeberg.[6]

14. Hülse, Walter: Virchows Arch. f. path. Anat. **225**:16, 1918.

15. Simonds, J. P.: Am. J. M. Sc. **166**:584, 1923.

in otherwise normal hearts. Variations were more frequent in the pulmonic than in the aortic ostium, and reduction was commoner than increase. Simonds offered three possible explanations of reduction. Antenatal or postnatal fusion of two cusps is suggested by finding one exceptionally large cusp with a ridge at the base of its sinus. A shift in the position of the aortic-pulmonary and distal bulb septum may be responsible for some of the two-cusped valves found in stenosed vessels. One of the four swellings may be absent or may regress at an early period. Four-cusp valves are infrequent; Simonds found reports of but five cases of four-cusped aortic valves, four of them in normal hearts. It is difficult to explain the acquisition of a perfectly formed, though often small, extra cusp, except on the basis of an interpolated fifth bulb swelling. If such a fourth cusp were present in a solitary aortic trunk, the picture of the ideal four-cusped common trunk would be closely imitated. No such case has been reported, to my knowledge. However, when the unique case reported by Glas [16] is considered, it is easy to see that with modification in the direction of atresia of the sixth arch structures, identification might be difficult. The heart described by Glas showed a large aorta with four cusps, in the "rider" position, while the small, three-cusped pulmonary artery rose from a stenosed pulmonic conus.

Alterations in the relationship of semilunar cusps to adjacent structures have a bearing on the interpretation of anomalies. Normally, each arterial ostium has one primarily septal cusp, the left posterior of the pulmonary artery, and the right anterior of the aorta. The other two pulmonic cusps are in relation to the base of the nonseptal (conus) wall of the right ventricle. The medial end of the posterior aortic cusp is in contact with the membranous part of the interventricular septum, while its lateral part and a small adjoining part of the left aortic cusp lie above and are continuous with the anterior (aortic) cusp of the mitral valve. The rest of the left cusp is continuous with the base of the nonseptal (conus) wall of the left ventricle.

Muscular Structures of the Right Ventricle and the Right Aorta.—On the basis of his phylogenetic studies, Spitzer [8] believed that in the mammal there is a rudimentary development of the second, right ventricular aorta of the reptile. He recognized as homologues of the muscle ridges of the inter-aortic septum of the reptilian heart the prominent muscle structures of the mammalian right ventricle. These structures were described by Tandler,[4] as the crista supraventricularis and the trabecula septomarginalis. Spitzer subdivided these muscle bands into the crista and trabecula proper, grouped as the crista aorticopulmonalis, and the anterior tricuspid ledge.

16. Glas: Jahrb. f. Kinderh. **49**:187, 1867.

The trabecula traverses the ventricle as a moderator band, from the lateral wall, near the acute margin and at a variable height above the apex, to the septum. Here the crista ascends as a smooth muscle band, to the base of the septal (left) pulmonic cusp. The ledge lies posterior and more or less fused with the crista. Its apical portion, lying behind the trabecula proper, is recognized from its intimate relation to the large lateral papillary muscle, which gives attachment to chordae from the anterior and posterior tricuspid leaflets. The septal part, commonly fused with the crista in the stem of the Y referred to in a foregoing paragraph, gives off several chordae for the medial tricuspid leaflet, and forms the base of the small septal papillary muscle of Lancisi, the medial attachment of the anterior tricuspid leaflet. Near the anterior margin of the membranous septum, this posterior part abruptly swings laterally and downward, in the direction of the large lateral papillary muscle. Near the base, this diverging muscle structure (arch of the crista of Tandler) separates the pulmonic ostium above from the anterior tricuspid leaflet, which is attached along its posterior wall. Thus, the almost complete muscular ring of the anterior tricuspid ledge demarcates the inflow (posterior) from the outflow (anterior) parts of the ventricle.

The importance of these structures in Spitzer's theory is that they identify the part of the ventricle belonging to the right aorta. The rudimentary conus of that vessel lies in a niche between these two structures at the base of the heart, directly opposite the conus of the left aorta. It is separated from that conus by the proximal bulb septum, from the inflow chamber by the ledge, and from the pulmonic outflow by the crista proper. Hence it ends blindly unless a septal defect is present. As has been seen, this region, the posterior part of the anterior septum of Rokitansky and the interaortic septum of Spitzer, is a common site of septal defects. When the septum is incomplete, and particularly when the aorta is shifted to the right, over the defect, important modifications are seen in the crista and ledge, and these changes may be the best clues one has as to the nature of the embryologic defect.

Torsion and Detorsion.—A factor that must be considered in the analysis of cardiac defects is the rôle of torsion, or of alterations in normal torsion, in relation to the picture produced. With lengthening and irregular widening of the primitive cardiac tube, a bending of the ventricular part develops. The winding of the ventricular loop produces a spiral rotation of the fixed ends of the tube. The normal direction of this winding is such as to produce a clockwise torsion of the arterial limb, and a counterclockwise twist of the venous end of the tube. Occasionally the direction may be reversed, giving the picture of mirror position dextrocardia, with or without heterotaxy. A torsion lag is a conspicuous feature of many cardiac malformations.

Spitzer stressed the rôle of detorsion in his phylogenetic theory of cardiac malformations. In his view, normal torsion, associated with local alterations due to the increased blood flow in the two circulations, is responsible for the definitive form of the mammalian heart. In other words, the development of a pulmonic circulation and normal torsion are essential for normal septum formation. At the arterial end the clockwise torsion finally reaches 180 degrees at the level of the semilunar cusps. In the embryonic stage it is documented, among other things, by the helical course of the swellings and septums of the trunk and bulb; in the definitive stage, by the clockwise winding of the pulmonary artery about the aorta. At the venous end, the counterclockwise torsion is most easily seen from the direction of the spirals of the interatrial septums, as seen from the right atrium.

Spitzer included the following features as landmarks of a lag in normal torsion: At the aortic ostium, the cusps and their identifying coronary ostia lag or are "displaced" in a counterclockwise direction. With extreme lagging there is a "transposition" of the two trunks, and one may see the "transposition" of the coronaries referred to heretofore. A defect in the interventricular septum is present, in the interaortic (conus) part. Spitzer interpreted this as due to opening up the conus of the right aorta, which may combine with the left ("common" or "rider" aorta) or may replace it (in "transposition of the great arterial trunks").

With increasing detorsion, the anterior tricuspid ledge grows smaller, and its divergence from the septum decreases. It finally loses its arch and comes to lie in the sagittal plane. As the ledge decreases and swings toward the septum, the attached anterior tricuspid leaflet naturally follows, until finally its medial part may stand in the same relationship to the semilunar cusps of the right or transposed aorta as the corresponding part of the anterior mitral cusp does to the normal aortic cusps. While the nonseptal part of the ledge becomes small the crista proper hypertrophies, and when aorta and pulmonary artery arise independently from the same (right) ventricle, it appears as a powerful muscle bundle ascending the septum and arching across the base to separate the two ostia. Thus it superficially resembles the arching part of the ledge. The more the pulmonic trunk is displaced to the left the larger the crista becomes, and the more it, too, approaches the sagittal plane. In so-called "crossed transposition," it and the septal part of the ledge may constitute a pseudoseptum, while only the rudiments of the true interventricular septum remain.

At the venous end, detorsion may be shown by disturbances in the relations of the two atria, and particularly by the presence of a widely patent foramen ovale with a poorly developed limbus (septum 2) and a shift of its valve (septum 1) to the left. With more extreme detorsion

there may be almost complete failure of septum formation, with persistence of a common atrioventricular ostium.

PARTIAL VS. TOTAL PERSISTENCE OF THE COMMON ARTERIAL TRUNK

The question of a qualifying adjective must be considered because cases have been reported as "total" or "complete" even in the presence of a well defined though abbreviated pulmonic trunk. Mönckeberg [6] and Feller [17] suggested that cases be considered as complete only when the spurs of the sixth arch have not fused, or when derivatives of the sixth arch are missing. This would include examples with an independent origin of the pulmonary arteries directly from the trunk, and those in which the lungs received blood only through collaterals. The cases in which there is very slight development of the septum could be qualified by such a term as "almost complete," to distinguish them from cases in which there are lesser septal defects, such as the two reported by Rokitansky [18] and the type of case reported and discussed by Hektoen.[19]

DIFFERENTIATION FROM SIMILAR ANOMALIES

The chief problem in establishing the identity of a common arterial trunk is due to the fact that superficially similar anomalies occur. These represent regression of one trunk after the aortic-pulmonary septum has formed and separated it from the other. Thus there are two types that must be distinguished, persistent solitary pulmonic trunk with aortic atresia, and persistent solitary aortic trunk with pulmonic atresia.

Solitary Pulmonic Trunk.—The anomalous heart possesses a single large arterial trunk, superficially combining the appearance of the aorta and the pulmonary artery. It should have three semilunar cusps and no coronary ostia. However, von Konstantinowitsch [20] reported an otherwise typical case in which one of the coronaries originated in a sinus of the pulmonic trunk. After giving off the pulmonary arteries at the usual level, the trunk goes over into the arch through an exceptionally wide ductus arteriosus. The impression conveyed is that of a continuous trunk, although in a number of reported cases the large branches of the arch appear to be crowded together or irregularly arranged. Aside from the absence of coronary ostia, the identifying feature is a small artery, the remnant of the aorta. This originates from the arch or from the root of one of its branches and follows the approximate course of the

17. Feller, A.: Virchows Arch. f. path. Anat. **279**:869, 1931.

18. von Rokitansky, C. F.: Die Defekte der Scheidewände des Herzens, Vienna, W. Braummüller, 1875; cited by Mönckeberg,[6] Abbott [2] and Keith.[25]

19. Hektoen, Ludvig: Am. J. M. Sc. **121**:163, 1901.

20. von Konstantinowitsch, W.: Prag. med. Wchnschr. **31**:657, 1906.

aorta with reference to the pulmonic trunk. At the base of the heart it gives off the coronary arteries and is inserted blindly above a left ventricle, which is often rudimentary.

Since Mayer's [21] report many examples of this anomaly have been doubly misinterpreted. The solitary pulmonic trunk has been regarded as a persistent common trunk. The aortic remnant, in which, obviously, the direction of blood flow is reversed, has been interpreted as a coronary artery, with an abnormally "high" origin. Since Rauchfuss,[22] Vierordt,[23] Herxheimer,[1] Abbott [2] and Mönckeberg [6] have emphasized the incorrectness of this interpretation, there is little excuse for failing to recognize this defect. A typical case has recently been reported by Shapiro.[3]

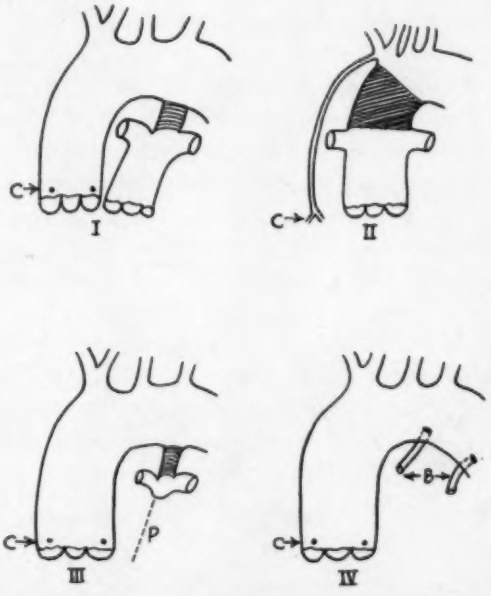

Fig. 1.—Diagrams of types of solitary arterial trunk: *I*. Normal separation of the aorta and pulmonary artery in a normally developing heart. *II*. Solitary pulmonic trunk, with an atretic aorta. The aortic remnant gives off the coronary arteries (*C*). *III*. Solitary aortic trunk, with an atretic pulmonic trunk. The pulmonic arteries receive blood through a patent ductus. The remnant of the pulmonic trunk may or may not be recognizable (*P*.) *IV*. Solitary aortic trunk, with bronchial arteries, and no recognizable sixth arch derivatives. In all four diagrams the ductus arteriosus is shaded. *C* indicates coronary ostia; *B*, bronchial arteries.

21. Mayer: J. d. Chir. u. Augenh. **10**:44, 1827.

22. Rauchfuss, C.: St. Petersb. med. Ztschr. **6**:370, 1864.

23. Vierordt, Hermann: Die angeborenen Herzkrankheiten, in Nothnagel: Spezielle Pathologie und Therapie, Vienna, Hölder, 1898, vol. 15, pt. 1, sect. 2.

Solitary Aortic Trunk.—In this anomaly, too, there is a single arterial trunk, which, with few exceptions, resembles the normal aorta. Thus one would expect three semilunar cusps and two coronary ostia. However, in two otherwise typical examples recently reported by Kugel [24] but one coronary stem was present. Also it is theoretically possible, as shown by Glas' [16] case, for four cusps to be present.

According to the degree of regression of the derivatives of the sixth arch, the pulmonary blood supply may vary. A well developed ductus arteriosus may persist, giving off the right and left pulmonary arteries. The atretic remnant of the pulmonic trunk may be present as a fibrous

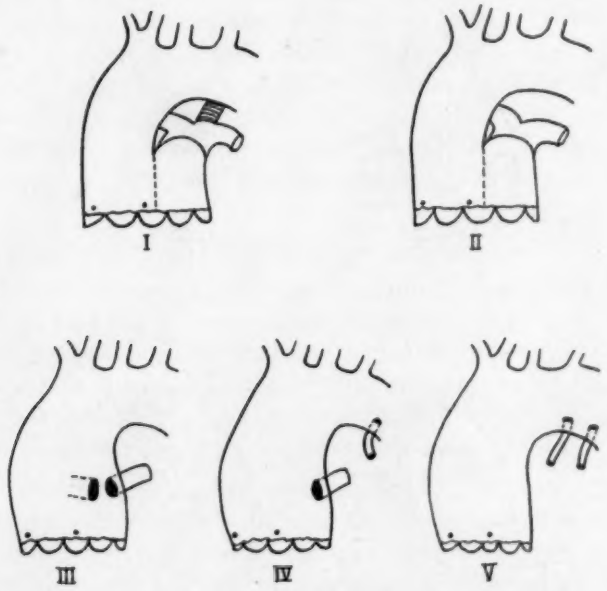

Fig. 2.—Diagrams of types of common arterial trunk: *I.* Partial common trunk with ductus arteriosus. *II.* Partial common trunk without ductus. *III.* Complete common trunk, with independent origin of two pulmonary arteries. *IV.* Same, transition form with one pulmonary and one bronchial artery. *V.* Same, with no sixth arch derivatives and only bronchial arteries.

cord, as in the case illustrated by Keith.[25] With more marked regression, the sixth arch vessels may be small, one of the pulmonary arteries may be missing, or there may be total disappearance of both sixth arches. Keith found this to be frequent in his cases. With diminished blood flow through the pulmonic channels, the collateral vessels, particularly the bronchial arteries, widen, and with atresia, the sole pulmonic arterial

24. Kugel, M. A.: Am. Heart J. **7**:262, 1931.
25. Keith, A.: Lancet **2**:359, 433 and 519, 1909.

blood supply goes through these vessels. A similar condition is seen in pulmonary atresia without cardiac deformity (Christeller,[26] Müller [27]).

Pulmonary and bronchial arteries may be distinguished by their origin and by their manner of entrance into the lungs. The former originate from the trunk, usually near the pericardial attachment, and enter the hilus close to and anterior to the main bronchus. The latter are often multiple and are variable in size. They originate irregularly from the arch and descending aorta and enter the hilus irregularly, often above or behind the bronchus, and frequently branch before entrance.

Identification of the Anomaly.—The typical example of solitary pulmonic trunk should be easily recognized. However, the aortic character contributed by a misplaced coronary, in a case like that of von Konstantinowitsch,[20] might cause confusion unless the aortic remnant is clearly recognizable.

The real difficulty is to distinguish the "complete" common trunk from solitary aortic trunk, when remnants of sixth arch structures are not found. Unless fibrous remnants of these structures are identified, a differentiation of the anomaly involving aplasia or very early regression of the sixth arch structures from that involving atresia and disappearance of the separated pulmonic trunk cannot be made on the character of the arterial trunk alone. The differentiation is further complicated by the fact that, in this group, as in most cases of common trunk, the aorta occupies the "rider" position. Thus the defect is a combination of various degrees of "transposition" with atresia of the pulmonic element. Another factor that must be considered is that in the hearts of adults, in this class, remnants of sixth arch structures that might have been recognizable in infancy may no longer be distinguished.

It remains to be seen whether a careful study of septal defects and of the muscular structures of the right ventricle will assist in the differentiation. On theoretical grounds these should give valuable information. If one found a well developed crista arching the vault of the ventricle, anterior to the solitary arterial ostium, this would suggest atresia of a "transposed" pulmonic trunk. The probability would be increased if the arch demarcated a small diverticulum, representing the pulmonic conus. With a common trunk, on the other hand, the crista should end at the base of the septum, beneath the anterior septal cusp.

REPORT OF A CASE

Clinical History.—A boy, born at full term at the Women and Children's Hospital, Chicago, on June 1, 1931, showed signs of congenital cardiac lesion at birth and atresia of the rectum. An operation was performed for production of an

26. Christeller, Erwin: Virchows Arch. f. path. Anat. **223**:40, 1916.

27. Müller, Leo: Ztschr. f. Kreislaufforsch. **19**:561, 1927.

artificial anus. The first bowel movement was one of meconium; it was followed by repeated stools of bloody mucus. There was persistent vomiting, with regurgitation of blood-stained fluid. The infant died on June 6.

Postmortem Examination.—Autopsy was performed by Dr. M. A. Southwick on the day of the infant's death. The findings were: a surgically created anus; a pocket-like invagination at the upper end of the natal fold; a palpable defect in the sacral arches (spina bifida occulta); a normal situs of the heart and other viscera; general cyanosis and venocapillary congestion; an abnormal arrangement of the mesenteries; a mobile cecum; bands between the gallbladder and the duodenum; multiple hemorrhages in the mucosa of the entire gastro-intestinal tract, with superficial ulceration in the colon; subcapsular hemorrhages in the liver, and pulmonary hyperemia and edema.

Histologic Examination.—The chief observations were capillary engorgement, marked passive hyperemia of the liver, with necrosis of the central zones, and pulmonary hyperemia and edema.

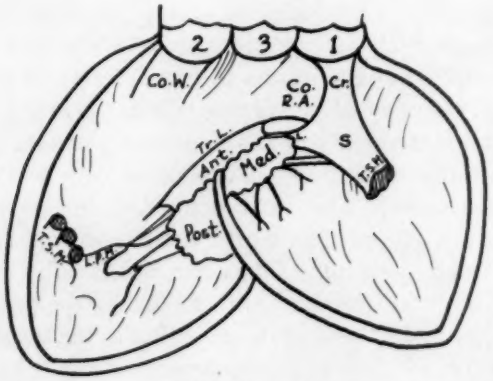

Fig. 3.—Diagram of a normal right ventricle of a child, aged 5 years. The numerals *1, 2* and *3* indicate cusps of the pulmonary artery; *Cr.*, the crista supraventricularis; *Tr.L.*, the anterior tricuspid ledge; *L.*, the papillary muscle of Lancisi; *L. P. M.*, the lateral papillary muscle; *S*, the fused septal part of the ledge and crista; *T. S. M.*, the trabecula septomarginalis; *Ant.* and *Med. Post.*, the tricuspid leaflets; *Co. W.*, the anterior wall of the pulmonic conus; *Co. R. A.*, the conus of the right aorta.

Description of Heart.—The length from the apex to the summit of the atria was 5.25 cm.; from the base of the arterial trunk to the apex, anteriorly, 4 cm.; from the atrioventricular groove to the apex along the acute margin, 4 cm., and along the obtuse margin, 2.75 cm. The maximum transverse diameter was 3.5 cm.; the anteroposterior diameter, 3 cm.

The heart was enlarged and rounded, and the apex was directed to the left. The anterior interventricular furrow appeared to be farther to the left than normal, while a proportionally large part of the presenting surface and the rounded apex was made up of the right ventricle. The two auricles stood in normal relation to the four chambers, although the left seemed small and was displaced a little posteriorly. There was no special prominence of the infundibular region of the right ventricle. In fact, the entire upper part of the anterior and lateral wall of this chamber appeared rounded and prominent. Only one large arterial trunk was

present, occupying most of the base of the heart. On its outer surface there was no indication of a subdivision. It bulged to the right immediately above its origin. From its posterior part, on the left, right and left branches were given off. The right passed behind the main trunk to enter the hilus of the right lung anterior to the main bronchus. The left passed to the left lung and entered similarly. From the angle between the two branches, apparently the pulmonary arteries, a third vessel emerged, and subsequently joined the main trunk. This vessel, 6 mm. long and appearing somewhat flattened, was a ductus arteriosus. The right half of the trunk continued into a normally constituted aortic arch, which gave off the innominate, left carotid and left subclavian arteries. The point of junction with the ductus arteriosus was the concavity of the arch, opposite to and just distal to the left subclavian. The subsequent course of the vessel was that of the normal descending aorta.

The ostium of the solitary trunk was equipped with four semilunar cusps. These were thick and fleshy, with irregular outer surfaces, covered with smooth endothelium. Instead of having a distinct nodulus, each cusp terminated in a point. The cusps were arranged so that two were anterior and two posterior. The right

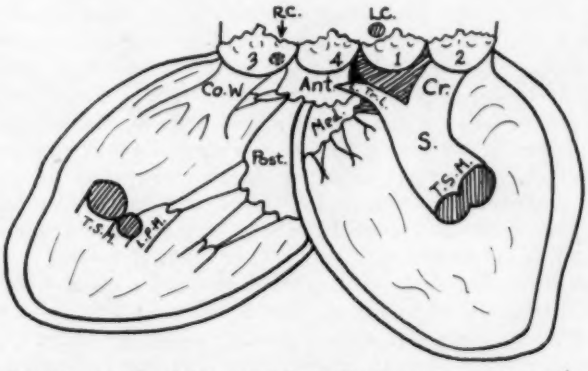

Fig. 4.—Diagram of the right ventricle in the case reported in this paper. The numerals *1* and *3* indicate undivided cusps; *4*, the "posterior" (aortic) cusp, and *2*, the "anterior" (pulmonic) cusp of the common trunk; *L. C.*, the left coronary ostium; *R. C.*, the right coronary ostium. The septal defect is represented by a shaded region beneath cusp 1, bordered posteriorly by the membranous part of the septum (black). Other structures are labeled as in figure 3.

anterior cusp was slightly in advance of the left. Numbering the cusps in a clockwise direction, cusp 1 (above which the left coronary arose) was left posterior; cusp 2, left anterior; cusp 3 (back of which the right coronary had its origin), right anterior, and cusp 4, right posterior. They were almost equal in size, cusps 1 and 4 measuring 7 mm. between the commissures; cusps 2 and 3, 6 mm. Reasoning from the position of the coronary arteries, cusp 2 (left anterior) represented the anterior pulmonary cusp; cusp 4, the posterior (noncoronary) aortic cusp, and cusps 1 and 3, the undivided "lateral" swellings.

The coronary ostia stood in their normal relationships to each other and to the cusps. Thus the left coronary rose just above the margin of cusp 1 (left posterior), and shifted slightly toward the commissure with cusp 4 (right posterior). The right coronary originated deep in the sinus of cusp 3 (right anterior) and close to its junction with cusp 4. The main stems of the arteries seemed long, particularly

that of the left, the origin of which lay farther back than usual. The left circumflex branch was short and soon terminated on the anterolateral surface of the left ventricle as an oblique descending branch. The left anterior descending branch was normal. The right coronary followed its usual course, gave off the posterior descending branch, and continued on to the posterior wall of the left ventricle.

Distally, the left half of the trunk was separated from the right by an archlike demarcation, obliquely placed, and slanting from the right posteriorly to the left anteriorly. The supports of the arch were seen as two very low ridges, extending from the vault to the arterial ostium. The posterior ridge met the commissure between cusps 1 and 4; the anterior, the opposite commissure between cusps 2 and 3. As viewed from above, these ridges described a clockwise spiral, but with less of a twist than would result if they reached the midpoints of cusps 1 and 3, the normal points of transection of the cusps and ostium. These ridges divided the ostium into two equal halves, 1.3 cm. each in circumference. Just above the ostium, in the bulging region, the right part measured 1.8 cm.; the left, 1.3 cm. As was indicated from the external examination, the right half continued into a normally constituted aortic arch and a descending aorta, the circumference of which at the level of the ductus arteriosus was 1.3 cm., while distally it increased to 1.5 cm.

The vault of the arch, 1.2 cm. above the bases of the cusps, cut off the shallow end of the left half of the trunk, from which the three sixth arch vessels originated. The arch was seen to be the margin of a low crescentic infolding. Below the level of the vault the mouth of the right pulmonary artery, 4 mm. in diameter, was seen. Concealed beneath the margin of the fold were the openings of the ductus arteriosus and the left pulmonary artery, which appeared to rise from the first part of the ductus. It was the same size as the right, while the ductus had a circumference of 6 mm. The inner surface of the latter was a little wrinkled. The relationships here certainly indicated the formation of an abbreviated pulmonic trunk, from which the normal derivatives of the sixth arch arose. However, the forerunners of the rudimentary septum, which indicated a division of the common trunk, failed to meet the midpoints of cusps 1 and 3, by a detorsion estimated at 45 degrees. Because of this lag, the left coronary ostium lay in the region marked off as belonging to the pulmonary artery. This is of interest because of the fact that one coronary, usually the left, has been reported as originating from the pulmonary artery. It would seem, however, that when this displacement is the only anomaly, it can be accounted for more easily by a displacement of the coronary anlage, than by a shift of the septum.

The right atrium received the two venae cavae and the coronary sinus in normal fashion. The eustachian valve was distinguishable as a fleshy fold, and a small thebesian valve was present at the mouth of the sinus. The left atrium received a common venous trunk, 4 mm. long, from the left lung, while the two right pulmonic veins entered independently. The primitive interatrial foramen was closed, but there was a wide foramen ovale (secundum). Its limbus was low, but was well demarcated, especially inferiorly. Its opening was partially guarded by a low crescentic fold (septum primum). This started on the upper anterior wall of the left atrium. At first it ran medially, inferior to and marking off the horn of the atrium that received the right pulmonic veins. It then curved backward and downward, gradually approaching the limbus, and ended on the anterior inferior wall of the atrium. The greatest width of the crescent was 4 mm., and it was separated from the limbus by a distance of 5 mm. above, decreasing to 0.5 mm.

The right ventricle was capacious, and its thick wall measured from 3 to 4 mm. Its muscle columns were conspicuous, and there were several features worthy of note in their arrangement. On the anterior wall of the conus beneath cusp 3

(right anterior), a heavy smooth muscle descended and soon broke up into trabeculae on the anterior wall. On the septal wall was a heavy Y-shaped muscle structure with a smooth surface. The vertical limb was short and broad, and slanted from anterior below to posterior above. Beneath a defect in the septum, it branched. The anterior limb formed the border of the defect anteriorly and ascended to the base of the septal semilunar cusp 2 (left anterior). The other formed the base of the defect posteriorly and, tapering gradually, skirted a small membranous part of the septum, and was attached to the anterior surface of the medial half of the anterior tricuspid leaflet. From its posterior margin, below its pointed end, several short chordae tendinae went to the medial tricuspid leaflet. From the base of the Y a very heavy muscle crossed the ventricular cavity as a short, thick moderator band, which appeared to be made up of two parts. The large anterior part was attached directly to the wall, while the smaller was attached to the base of a large lateral papillary muscle. Comparison with the normal showed that the large moderator band undoubtedly was the trabecula septomarginalis. Its small posterior

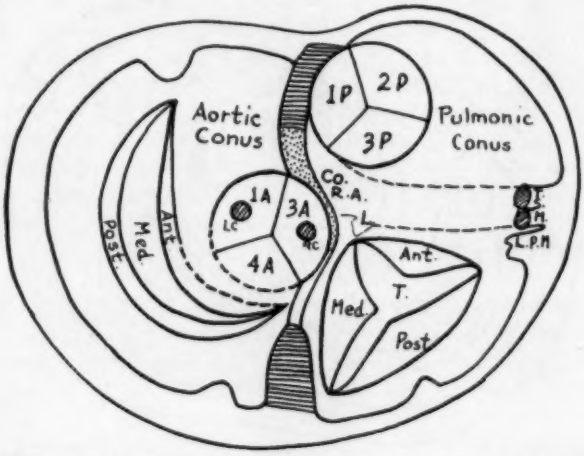

Fig. 5.—Diagram of a normal heart, showing the relations of the valve orifices to adjacent structures. *A* indicates the aortic cusps; *P*, the pulmonic cusps. The shaded regions of the interventricular septum indicate the anterior and posterior muscular portions; the stippled region, the interaortic (muscular) septum; the unmarked region, the membranous septum. The dotted lines at the bases of the aortic and anterior mitral cusps show the region of fusion.

part, in relation with the papillary muscle, represented the lateral apical part of the anterior tricuspid ledge. Both the ledge and the crista supraventricularis were fused where they ascended the septum, in the stem of the Y. Beneath the defect, the crista forked anteriorly and ascended to the base of cusp 2. This is contrary to its behavior when the arterial trunks are transposed; then the hypertrophied crista traverses the base like an arch, between the two ostia. The ledge turned posteriorly and soon ended in a point, which seemed to represent an elongated muscle of Lancisi. In other words, the ledge had lost its normal divergent arch.

Correlated with the hypoplasia of the tricuspid ledge there were striking changes in the relations of the anterior tricuspid leaflet. It appeared as a short cusp, with its medial end shifted toward the sagittal plane, and throughout most of its length it was applied directly to the base of semilunar cusp 4 (right posterior); i. e., it

stood in the same relation to the noncoronary aortic cusp as does the anterior mitral leaflet in the normal heart. Associated with its decrease in size, loss of obliquity and shift of plane was its detachment from the large lateral papillary muscle. Its lateral attachments were a few short chordae, lateral to the muscle bundle beneath cusp 2 (right anterior), originating close to the base of the heart.

The relations of the posterior and medial tricuspid cusps were not greatly altered, though the medial was small and the posterior relatively large. There were two well defined groups of papillary muscles. Attached to the posterior cusp were the chordae from the large lateral muscle described, and others from a second smaller group, lying behind it. The chordae of the medial cusp rose from a group of small papillary muscles situated high on the posterior septum, and from the septal part of the tricuspid ledge, as described.

The left ventricle had a relatively small cavity and a wall from 4 to 6 mm. thick. The muscle columns were small and flat, and the vertically directed aortic conus sloped toward the septal defect. Unlike the normal, none of the conus lay

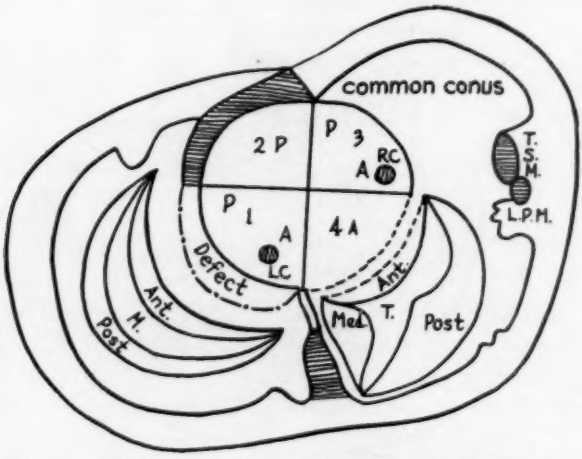

Fig. 6.—Diagram of the heart in the case reported in this paper, showing the relations of the orifice of the common trunk to adjacent structures. *A* indicates the aortic and *P* the pulmonic elements of the cusps. A defect is represented in the interaortic part of the interventricular septum, beneath cusp 1. The dotted lines show fusion of cusp 4 with the anterior tricuspid leaflet.

anterior to the mitral area, but it appeared both flattened and shortened anteroposteriorly, so that the anterior mitral cusp hung like a curtain against the defect. The basal attachment of this cusp was entirely muscular; i. e., it was not fused with the base of the aortic cusps as in the normal heart.

The interventricular septum showed a helical twist. The base measured 1.5 cm. in a straight line, and 2.2 cm. along its curving margin. It sloped from right above posteriorly to left below anteriorly. At the base, the greatest convexity was anterior and directed to the left. At the apex, the convexity was toward the right, and the tip of the left ventricle, lying in advance of the right, appeared as if hollowed out of the septum. The greatest breadth of the septum, 1 cm. below the base, was 3 cm., and its average thickness was 5 mm.

The septal defect was pyramidal in shape. Its base, along the lower margin of semilunar cusp 1 (left posterior), measured 7 mm., and its height at the

branching of crista and ledge was 5 mm. As stated, its lower margins were these two muscle structures, which were fused smoothly with the rest of the anterior septum. At its posterior angle it was in relation with a small part of the base of cusp 4 (right posterior) at its junction with the anterior tricuspid leaflet. And just behind this, it bordered the small membranous part of the septum, interposed between it and the posterior muscular septum. Hence the base of the septum, from front to back, was made up of an anterior muscular part, measuring 8 mm., the defect, 7 mm., and a posterior septum, 7 mm., the anterior membranous part of which measured about 2.5 mm. It should be noted that the small membranous septum was normally placed beneath the attachment of the medial tricuspid leaflet. A needle passed from the point where it joined the defect emerged in the right atrium, below and anterior to the mouth of the coronary sinus. These relationships indicate that the defect was in the posterior part of the anterior septum of Rokitansky, the interaortic septum of Spitzer.

The basal relations of the semilunar cusps were as follows. The base of cusp 1 (left posterior) bridged the septal defect, as described. A small part of the adjacent border of cusp 4 (right posterior) bordered the defect, in the region of the membranous margin, beyond which the base of this cusp was closely applied to the base of the anterior tricuspid leaflet. Cusp 3 (right anterior) lay above the base of the anterior (conus) wall of the right ventricle. Cusp 2 (left anterior) was applied to the base of the anterior part of the interventricular septum. Thus two cusps, instead of one, were in relation to the septum, while only cusp 1 had any appreciable relation to the defect. Almost three fourths of the entire circumference belonged exclusively to the right ventricle, and only half of the cusp that bridged the defect was developmentally an aortic cusp. Taking the positions of cusps 2 and 4 as indexes, the arrangement indicated a detorsion defect, probably of slightly more than 45 degrees.

Summary: Summarized, the observations on the heart showed a normal situs; a four-chambered heart; partial (almost complete) persistence of the common arterial trunk; a rudimentary aortic-pulmonary septum, delimiting an abbreviated pulmonic trunk, which gave off in normal fashion right and left pulmonary arteries and a ductus arteriosus; four semilunar cusps, with normal relations of cusps and coronary ostia, position of cusps and ostia indicating a lag in a counterclockwise direction of about 45 degrees from normal; polypoid overgrowth of the semilunar cusps; halving of the trunk ostium by forerunners of the aortic-pulmonary septum, their positions indicating a shift of 45 degrees in a counterclockwise direction from the expected line of descent, i. e., total detorsion of the septum of about 90 degrees; location of the left coronary ostium in the pulmonic part of the trunk; general course of the coronaries normal; a defect in the base of the interventricular septum, in the posterior part of the anterior septum; "rider" position of the common trunk, with major origin from the right ventricle; hypertrophy of both ventricles, particularly the right; opening up of the right aortic conus, with decrease in the size of the left aortic conus and loss of its anterior (premitral) part; dissociation of the anterior mitral cusp from the base of the arterial trunk, with attachment of the medial part of the anterior tricuspid leaflet to the base of the trunk; shift of the position of the latter cusp toward the sagittal plane, with high attachment of its lateral end to the basal part of the ventricular wall; fusion of the medial end of this cusp with the elongated papillary muscle of Lancisi; absence of the basal arch of the anterior tricuspid ledge; hypertrophy of the trabecula septomarginalis and the septal parts of the crista supraventricularis and the anterior tricuspid ledge; a remnant of the membranous part of the interventricular septum in normal position at the posterior margin of the defect and in relation to the medial end of the

anterior tricuspid leaflet; hypertrophy of the right atrium; small left atrium, its auricle displaced backward; wide patency of the foramen ovale (secundum); hypoplasia of both the limbus and the valve, with displacement of the valve (septum primum) to the left; common right pulmonic venous trunk.

REVIEW OF THE LITERATURE

Part of the difficulty in an attempt to survey the literature on the common arterial trunk arises from confusion of nomenclature. In some reports the term "persistent common arterial trunk" appears to be used in the sense that the trunk is common to both ventricles. In the older literature many cases are reported as "persistent arterial trunk" without reference to the developmental features. In other reports the data are incomplete, particularly with reference to such important identifying features as the coronary blood supply and the arrangement of the semilunar cusps. In others there is no description of the arterial supply of the lungs, a knowledge of which is essential for diagnosis. In very few is there any mention or description of the muscle bundles of the right ventricle. Another fact that must not be forgotten is that true cases of persistent common trunk may be hidden under the caption of pulmonic atresia.

Keith [25] believed that this anomaly was very rare, and stated that he had never encountered an example, personally. In his discussion of the condition, he presented a picture of one of Rokitansky's two cases. This shows a partial defect, with the lower end of the septal margin at the level of the interventricular defect. Herxheimer [1] listed forty-three cases, but many of them have been positively identified as examples of solitary aortic or pulmonic trunk. His description of a "typical" case, in a specimen from the Heidelberger Institute, permits identification as an example of solitary aortic trunk. The "pulmonary" artery from the arch, giving off right and left pulmonic branches, undoubtedly represents a ductus arteriosus. Abbott,[2] as has been stated, found twenty-three cases, fourteen of which she analyzed as instances of the "complete" defect. The specimen from the McGill Museum, described by her, had three semilunar cusps and two coronary ostia. However, she stated that the blood supply to the lungs was unknown, which makes positive identification impossible. Mönckeberg [6] discussed the features of his anomaly and the difficulties of identification. He used as an example Wirth's [12] specimen, the original report on which is difficult of access. This example fulfils many of the criteria.

A number of excellent critical reviews have appeared in recent years. Those of Hülse,[14] Siegmund [28] and Feller [17] are especially valuable. Hülse quoted the analyses of Pietzch [13] and Wirth,[12] who admitted only

28. Siegmund, H.: Ztschr. f. Kreislaufforsch. **20**:65, 1928.

the cases of Buchanan [29] and Preiz [30] and Wirth's own case as true instances of total persistence of the common trunk. Hülse added one case and included two cases reported by Wenner [31] and, as probable, one reported by Wright and Drake.[32] Siegmund added three cases, two of his own and one reported by Klemke.[33] Feller added Zimmermann's [34] case and four of his own, three of them cases of "partial" defect. To these should be added the case of Dickson and Fraser,[35] possibly those of Finley [36] and Grant,[37] and certainly that of Santa Cruz [38] and the case reported in this paper. The completed list includes but twenty cases that have been regarded by recent reviewers as probable instances of the anomaly under consideration. It does not include cases with such minor defects as those seen in the group discussed by Hektoen,[19] nor those with partial, but almost complete, septums, such as Rokitansky's [18] two cases.

Analysis of Reported Cases: Group A. Persistent Common Arterial Trunk with Four Semilunar Cusps.—This group includes four cases of partial (almost complete), and one of complete, common trunk. They have certain features in common. All were found in infants, the oldest aged 2½ months, who had shown cyanosis and other signs of congenital heart disease. In each case, the four semilunar cusps showed the changes sometimes referred to as "fetal endocarditis"; that is, they were variously described as firm and thick, with warty or polypoid surfaces. Histologic studies showed only noninflammatory proliferative changes. Feller [17] called attention to the fact that they resembled normal fetal cusps. In all of these cases, the heart had four chambers, with a defect in the interventricular septum, anterior to at least a part of the membranous portion of the septum. (Santa Cruz made no reference to this feature). In other words, the defect was in the posterior part of the anterior septum of Rokitansky, the interaortic septum of Spitzer. In each case, the common trunk rode the defect, in most instances shifted to the right so that the major part of its ostium was related to the right ventricle. The part related to the defect and thus to the left ventricle was usually in the posterior left quadrant. There was a correlated hypertrophy of the heart, predominantly of the right chambers. The

29. Buchanan, G.: Tr. Path. Soc., London, **15**:89, 1864.
30. Preisz, Hugo: Beitr. z. path. Anat. u. z. allg. Path. **7**:247, 1890.
31. Wenner, Otto: Virchows Arch. f. path. Anat. **196**:127, 1909.
32. Wright, J. H., and Drake, A. K.: Tr. A. Am. Physicians **18**:272, 1903.
33. Klemke, W.: Centralbl. f. allg. Path. u. path. Anat. **36**:307, 1925.
34. Zimmermann, H. M.: Am. J. Path. **3**:617, 1927.
35. Dickson, W. E. C., and Fraser, J.: J. Anat. & Physiol **48**:210, 1910.
36. Finley, K. H.: Am. J. Path. **6**:317, 1930.
37. Grant, H. H.: Am. J. M. Sc. **86**:149, 1883.
38. Santa Cruz, J. Z.: J. Philippine Islands M. A. **5**:295, 1925.

foramen ovale was open, except in the oldest infant. With the exception of Preisz' case, the arch was normally formed, but for the variant of a right aortic arch in one of Feller's cases. A histologic study of the myocardium by Feller showed only hypertrophy of myocardial fibers and a little interstitial fibrosis. In all cases, the situs was normal, and the lungs were normally formed. The special features of each case are as follows:

Preisz'[30] case was that of a girl 9 hours old. The observations were: four semilunar cusps, two posterior and two anterior; a coronary artery with distribution to the right ventricle from the left anterior sinus; a coronary for the left side of the heart from above the commissure between the posterior cusps; a bulging trunk, its division into two parts indicated by a shallow groove; the right part, small, flattened, giving off two carotid arteries and the right subclavian artery; from the posterior wall of the left part, two arteries to the right lung, at the level of the arch branches; a little further, on the same side, an artery to the left lung, and opposite, the left subclavian; further course like that of the normal descending aorta; a foramen ovale with a perforated membrane displaced to the left and widely patent; a tricuspid valve "normally formed," but with the anterior cusp in relation to the anterior margin of the septum membranaceum; a powerful muscle bundle springing from the anterior wall of the right ventricle (trabecula septomarginalis?); an interventricular foramen below the middle of the left posterior cusp, therefore with less than a quarter of the circumference related to the left ventricle.

There are certain puzzling features to this case. The groove probably represented the anlage of the aortic-pulmonary septum. It is hard to explain why the right, obviously aortic, half seemed to end with the three arch branches, while the trunk appeared to continue from the left, pulmonic half. The most rational explanation would be that the sixth arch structures at least partially differentiated, but only a short wide ductus persisted, taking the place of an atretic distal aortic arch. The relation of the left subclavian to the ductus suggests this, as, according to Abbott,[2] the apparent origin of this vessel from the distal end of the ductus is not an infrequent anomaly. Consideration of Feller's case 3 makes this interpretation probable. The arteries to the lungs were probably, from their origin, bronchial arteries, though there is no reference to their mode of entrance into the lungs. Another puzzling feature is the relationship of the coronary arteries. It seems probable that the one arising over the commissure belonged to the right posterior cusp. The exact origin of the one from the left anterior sinus is not given, but the shift of the posterior would seem to indicate that the left posterior cusp represented the noncoronary cusp. Feller,[17] however, concluded that it was much more likely that the posterior (left) coronary was displaced to the pulmonic field (as in my case), and that the right anterior cusp represented the noncoronary aortic cusp, which would indicate a severe detorsion defect of from 135 to 180 degrees. The alternative explanation would require a contratorsion, of which there was no evidence in the position of the viscera. The evidence, then, is in favor of

a diagnosis of total persistence of the common trunk, with a persistent ductus arteriosus compensating for an atresia of the distal aortic arch, and with a severe detorsion defect, but without transposition of the coronaries (evidenced by the long course of the left coronary, about the left side of the trunk).

Santa Cruz'[38] case was that of a boy 63 days old. He found four semilunar cusps, anterior and posterior, and right and left; a well defined aortic-pulmonary septum descending to 1 cm. above the cusps, with a forerunner indicating a bisection of the right cusp; a location of the pulmonic part of the trunk anteriorly and to the left, which gave off from its posterior wall the two pulmonary arteries; an absence of the ductus arteriosus; a normal arch and descending aorta.

This description lacks certain important details, as there is no mention of the coronary arteries, nor of the relation of the septal defect to the cusps and the membranous septum. However, it is sufficiently detailed to identify this as an example of a partial persistence of the common trunk. The position of the forerunner, bisecting the right cusp, gives a clue to the degree of detorsion, which must be slight, probably less than 20 degrees.

Feller's[17] case 1 was that of a prematurely born girl at 8 months who lived two days. His observations were: four semilunar cusps, two posterior and two anterior; a left coronary artery from the sinus of the left posterior cusps and a right coronary from the right anterior cusp, both shifted toward the commissures with the right posterior (i. e., noncoronary) cusp; a distinct aortic-pulmonary septum marking off a short pulmonic trunk, which gave off two normal pulmonary arteries; absence of the ductus arteriosus; definite forerunners of the septum, the anterior (left) stopping high and the posterior (right) stopping above the middle of the left posterior cusp; absence of abnormalities in the arch and descending aorta, except for a right instead of a left course; a slightly developed "crista supraventricularis" (arch of the tricuspid ledge?).

The description given is unquestionably that of a partial common trunk. The cusps are identified from the "normal" origin of the coronaries, and their position indicates a detorsion defect of a little less than 45 degrees. The long forerunner of the aortic-pulmonary septum lies in the expected position for bisecting the left posterior cusp; i. e., its detorsion coincides with that of the trunk.

Feller's[17] case 4 was that of a girl 2½ months old. The observations were: four semilunar cusps, two posterior and two anterior; a left coronary artery from the sinus of the left posterior cusp, almost above the commissure with the right posterior cusp; a right coronary artery from the posterior end of the right anterior cusp; a septal defect beneath both posterior cusps, so that nearly half of the circumference was related to the left ventricle; a distinct aortic-pulmonary septum, with forerunners high above the ostium; a short pulmonic trunk, giving off two normal pulmonary arteries and a still patent ductus arteriosus; a well formed "crista"; a small muscle band from the septum (muscle of Lancisi?) forming part of the attachment of the anterior tricuspid leaflet; a closed foramen ovale; a normal arch and descending aorta.

Here, too, the description is that of a partial common arterial trunk, with a detorsion defect similar to that in the preceding case, of probably less than 45 degrees.

The case reported in this paper was that of a boy 6 days old. For details, see the earlier summary. In general features, this case resembles Feller's cases 1 and 4, but with slightly greater detorsion—more than 45 degrees. As in Feller's case 4 there is a ductus arteriosus. It shows also a further lag of the aortic-pulmonary septum of 45 degrees with a consequent displacement of the left coronary to the pulmonic field. It is impossible to compare other features, but in my case there is additional evidence of greater detorsion at the venous end, in the more primitive state of the atrial septums.

Group B. Persistent Common Arterial Trunk with Three Semilunar Cusps and a Rudimentary Fourth Cusp.—The general characteristics of the first two of the three cases in this group are very similar to those of group A.

Buchanan's [29] case was that of a girl 6½ months old. The observations were: three cusps, a left anterior and a left posterior and a large right, with a ridge indicating a subdivision of this cusp into anterior and posterior halves, so that it "looked much like two imperfect valves joined together"; same "knotted" consistency of cusps as in group A;; two large pulmonary arteries given off from the common trunk before it left the pericardial sac from "above the right coronary"; absence of a ductus arteriosus; a normal arch and descending aorta, except for the right course; a trunk from both ventricles; a wide open foramen ovale. The exact relation of the ventricular septal defect is not stated. No description of the coronary arteries is given.

The data do not permit the identification of the cusps and the degree of detorsion. However, the independent origin of the pulmonary arteries from the first part of the trunk makes it probable that this is an example of complete persistence of the common trunk.

Feller's [17] case 2 was that of an infant several months old. The observations were: three semilunar cusps, anterior, posterior left and posterior right; thick, slightly irregular cusp margins; partial fusion of the two posterior cusps at their commissure; indicated subdivision of the right posterior cusp; a well defined aortic-pulmonary septum, with forerunners dividing the posterior left cusp and the anterior part of the posterior right cusp; a left coronary artery between the left forerunner and the posterior commissure; a right coronary artery in the restricted region between the right forerunner and the ridge indicating division of the right posterior cusp; a corresponding decrease of the posterior (aortic) part of the trunk orifice, and of the small posterior part of the trunk, which gave off the innominate and left carotid arteries, then went as a narrow (2 mm.) aortic arch to join a large ductus; this and two normal pulmonary arteries derived from the anterior part of the trunk; the left subclavian given off at junction of the ductus with the arch; an interventricular septal defect at the base of the left posterior cusp; below it a powerful muscle bundle running from the septum to the wall of the right ventricle (trabecula?); a poorly developed "crista supraventricularis."

This case appears to be a combination of partial persistence of the common trunk, with stenosis of the aortic element of the trunk and of the distal arch. There is a compensatory enlargement of the pulmonic part of the trunk and of the ductus. The arrangement of the forerunners of the aortic-pulmonary septum and of the coronary arteries would place the small fourth, noncoronary cusp but a little short of its normal position. This would indicate a degree of detorsion less than in Feller's cases 1 and 4 and mine, and not far from that in Santa Cruz' case, which this case most closely resembles in degree of septum formation. There is interesting confirmation of this in the published photograph. Beneath the septal defect, as in my specimen, is a Y-shaped septal muscle band which resembles the similar structure in my case, even to the relationship of the small papillary muscle of Lancisi. The chief point of difference is that a thin, rounded muscle passes in the same direction as the normal arch of the tricuspid ledge. In my case, involving a greater detorsion, the basal part of the diverging limb of the ledge had disappeared. It seems likely that Feller's references to a small "crista" apply to the arch of the ledge.

Feller's [17] case 3 (in many details this case is very unlike the preceding cases) presented: a very large bulging arterial trunk; three semilunar cusps, right posterior, left posterior and anterior; an indicated division of the right posterior cusp, as in the preceding case; a "left" coronary ostium from near the posterior commissure of the left posterior cusp; a "right" coronary ostium just anterior to the ridge dividing the right posterior cusp; absence of a trunk septum; just proximal to the arch, from opposite sides of the trunk, two arteries that enter the right and the left lung in the normal positions of pulmonary arteries; absence of the ductus arteriosus; a normal arch and descending aorta; an interventricular defect unlike the preceding one; beneath the semilunar cusps a powerful muscle arch, forming the upper septum; below its concave lower margin, a defect, bordered below by a muscular septum; wide open foramen ovale primum and secundum; persistence of the left superior vena cava; a common arterioventricular ostium, with a three-cusped valve.

The analysis of this case is difficult. It probably represents a complete persistence of the common trunk, while the high origin of the pulmonary arteries indicates a complete failure of descent, as well as of fusion, of the aortic-pulmonary spurs. A possible clue to the nature of the anomaly is found in Spitzer's [8] analysis of the anomaly of "mixed transposition." Furthermore, Feller's description of the septum in his case shows a considerable similarity to the septum of a specimen illustrating this anomaly, which I have studied. The chief difference is that in his case the solitary trunk rose exclusively from the right ventricle, and the only communication with the left was through the low septal defect, while in my specimen the two trunks rose from opposite sides of the heavy muscular septum, with a low defect. Spitzer's interpretation is that the apparent septum was really a pseudoseptum, resulting from

the fusion and hypertrophy of the crista and the tricuspid ledge, which appeared with extreme detorsion.

Feller's own interpretation is that the small indicated right posterior cusp was the noncoronary cusp, a position that would indicate normal torsion. A much more probable conclusion is that the anterior cusp was the noncoronary cusp, and that there was almost complete (180 degrees) detorsion. One would also have to assume a transposition of the coronary arteries, the apparent left being the right, and the apparent right, the left. And further there was an indicated restriction of the pulmonic part of the ostium, a common phenomenon in detorsion defects. It is interesting that such a restriction should be indicated prior to descent of the aortic-pulmonary septum. There is confirmatory evidence in favor of a severe detorsion defect and of the foregoing theory in the various malformations at the venous end of the heart.

Group C. Possible Cases of Persistent Common Trunk with Three Semilunar Cusps.—From all of the evidence given, from the occurrence of cases such as those in the preceding group, which show a transition from four to three cusps, and from the occurrence of cases such as Rokitansky's, with three cusps and a well developed but incomplete trunk septum, it is evident that there may be numerous examples of persistence of a common trunk, with but three cusps. In the reported cases the evidence is often far from complete, particularly in the instances in which the blood reaches the lungs only through collateral channels. I have found but five probable and two other possible cases, in which the common trunk is identified by its giving off of true pulmonary arteries.

Grant's [37] case was that of a mulatto girl 16 years old. The observations were: a solitary trunk with three semilunar cusps, posterior, and right and left anterior; two coronary arteries, both from the right anterior sinus of Valsalva; two arteries to the lungs, leaving the trunk at the pericardial attachment, and a defect in the interventricular septum. No other abnormalities were described.

Siegmund's [28] case 2 was that of a girl 12 days old. The observations were: an almost bilocular heart, with only a rudimentary interventricular septum; absence of atrial septums; a common atrioventricular opening; a trunk with three cusps; two coronary arteries from the sinuses of the "right and left" cusps; two arteries arising independently 1 cm. above the semilunar cusps and entering the lungs in the manner of pulmonary arteries; no trace of an aortic-pulmonary septum or ductus arteriosus; a normal arch and aorta.

Klemke's [33] was that of a laborer, aged 25 years. The observations were: a trunk with three cusps, anterior, and right and left posterior; two coronary arteries, arising from the sinuses of the anterior and posterior left cusps; two arteries arising from the posterior left part of the trunk, a short distance above the cusps, and entering the lungs like pulmonary arteries, the margins of the ostia of which appeared as two convex arches, the lateral ends lost on the arterial wall, the medial fused (i. e., an interpulmonic spur formed); absence of ductus arteriosus; a normal arch and descending aorta; an interventricular defect in the "anterior and middle thirds" of the membranous septum; the trunk in a "rider" position; slight patency of the foramen ovale.

Wirth's [12] case was that of a boy who died one hour post partum. The observations were: three semilunar cusps, anterior and right and left posterior, thick at the margins; two coronary arteries from the posterior right and the anterior cusps; an artery leaving the trunk 1.5 cm. above the cusps and entering the left lung in the position of a pulmonary artery; absence of a right pulmonary artery and of a ductus arteriosus; two bronchial arteries to the right lung, from the descending aorta. Other features were in general like those of cases in groups A and B.

Dickson and Fraser's [35] case was that of a boy 4 months old. The arrangement of the cusps (and coronaries?) was as in Wirth's case. The only important difference was the presence of the right as the solitary pulmonary artery, and of bronchial arteries to the left lung.

The most probable explanation of the cases in this group is that they represent a complete persistence of the common arterial trunk. As far as is known, both coronary arteries are never transposed to the pulmonic trunk, so the alternate identification of the cases as examples of aortic atresia is very unlikely. The identification is most complete in Klemke's case, in which an interpulmonic spur had developed. It is interesting, too, that the patient in this case was the only one in the entire series who survived to adult years. This fact and the clinical history indicate that, clinically, the defect was not unlike pulmonic atresia. It is also of interest that the last two cases form a transition between those of complete common trunk with two independent pulmonary arteries, and the group with only bronchial arteries.

Wenner's [31] case 5 was that of a girl 3 days old. The "pulmonary" arteries were described as originating high. The one to the right lung rose opposite the right innominate; that to the left, a little higher. No description is given of the manner of entrance to the lungs. The general features were like those in groups A and B. This information makes it highly probable that these arteries were bronchial instead of pulmonary arteries.

Wenner's [31] case 6 was that of a boy 2½ days old. The observations were: a monoventricular heart with a small left atrium, a wide foramen ovale, a persistent left superior vena cava and atresia of the atrioventricular orifice; two pulmonary arteries given off from the wide arterial trunk; only one coronary artery.

From the information given, I do not believe that it is possible to classify this case exactly. Also, there is a resemblance of its main features to those of von Konstantinowitsch's [20] specimen. It is possible that this case, too, may represent a solitary pulmonic trunk, with a misplaced coronary ostium.

The remaining cases are all examples of single arterial trunks, with no recognizable derivatives of the sixth arch (Hülse,[14] Zimmermann,[34] Siegmund [28] [case 1], Finley [36] and Wright and Drake [32]). The blood supply to the lungs was not known in the last case, and a small vessel from the concavity of the aortic arch may have been either a ductus arteriosus or a bronchial artery. One outstanding feature is that in the first four of these cases the patients had lived for periods of from eighteen to thirty-three years. The possibility of disappearance of

atretic remnants that might have been recognizable in infancy can not be excluded. I believe that on available evidence the positive identification of these cases and those of Wenner as instances of common arterial trunk is impossible. But it is also possible that a careful study of the general cardiac structure, and especially of the muscular structures of the right ventricle, as interpreted by Spitzer, may give criteria for positive identification.

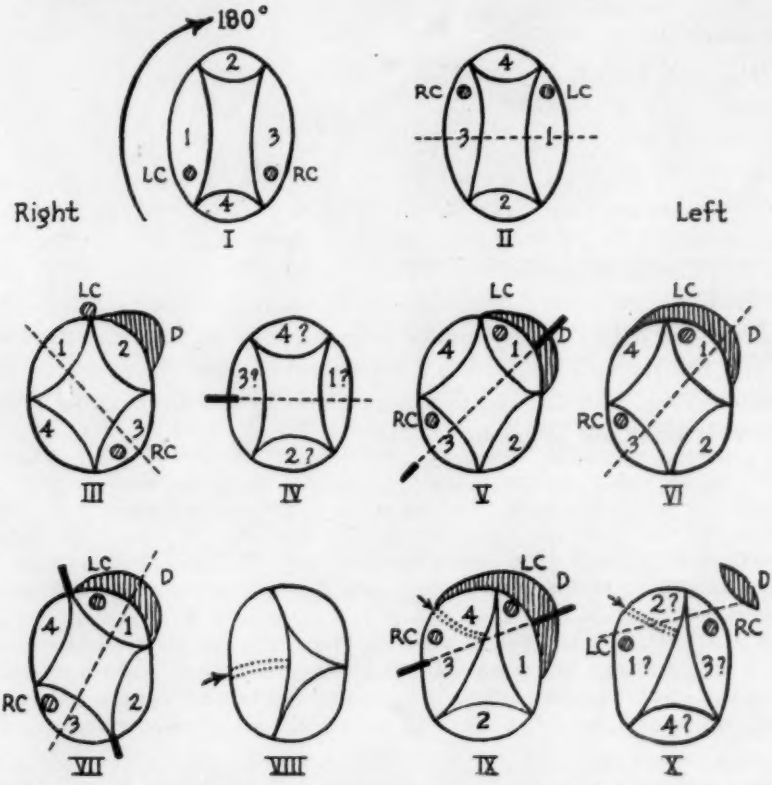

Fig. 7.—Diagrams showing the arrangements of the cusps in the reported cases of common trunk: *I.* Normal arrangement before rotation. *II.* Normal arrangement after torsion of 180 degrees. *III.* Preisz' case. *IV.* Santa Cruz' case. *V.* Feller's case 1. *VI.* Feller's case 4. *VII.* Case reported in this paper. *VIII.* Buchanan's case. *IX.* Feller's case 2. *X.* Feller's case 3. The dotted line indicates the theoretical position of the trunk septum. The heavy lines show the position of septal ridges, where present. The double dotted lines show the rudimentary subdivision of a cusp. *D* indicates a defect in the interventricular septum, and *L. C.* and *R. C.*, the position of the left and right coronary ostia.

CRITERIA FOR IDENTIFICATION OF THE COMMON ARTERIAL TRUNK

From a study of the developmental factors concerned it is obvious that there is no one typical picture of the common arterial trunk. How-

ever, from a study of these factors and of the features of a series of cases illustrating different types of this anomaly the general characteristics can be formulated.

1. The primary requirement is that only one large arterial trunk leaves the base of the heart. The possibility of an atretic companion must be excluded by a careful search for a small vessel or a fibrous cord in regions where such remnants might be expected to persist. The size of the trunk should approximate the size of the two arterial trunks combined. Obviously this requirement cannot be rigidily enforced. Size may be modified by decrease (stenosis) of the realm of one of the arteries, while a solitary trunk may reach a considerable size in compensating for its atretic companion.

2. The arterial trunk must combine the features and functions of both the aorta and the pulmonary artery, on the one hand giving off the coronary and systemic arteries, and on the other supplying blood to the lungs. When the sixth arch structures fail to develop or when they regress early, the arterial blood must reach the lungs through collateral channels. When the sixth arch spurs are present but fail to fuse to form a septum, the pulmonary arteries rise independently from the ascending trunk. In either of these cases, the anomaly is "total" or "complete." In the "partial" anomaly, a rudimentary septum delimits an abbreviated pulmonic trunk, which gives off the pulmonary arteries and occasionally a ductus arteriosus. Externally, the septum may be indicated by a groove. From within it appears as a low ridge, or a distinct arched fold, stopping at varying heights above the ostium. It frequently sends ridges as forerunners along the line of descent, and these may reach the ostium, indicating a division into aortic and pulmonary realms. These ridges may occasionally deviate from the expected lines of descent.

3. An interventricular septal defect is always present. This is commonly an opening in the septum of the cardiac bulb, anterior to a residuum of the membranous septum, i. e., in the interaortic septum of Spitzer or the posterior part of the anterior septum of Rokitansky. With extreme detorsion it may lie lower, but still in the conus septum (septum spurium); or there may be complete failure of development and fusion of the elements making up the ventricular septum.

4. The trunk, commonly in the position of the "rider" aorta, with varying degrees of shift to the right, may, with extreme detorsion, rise solely from the right ventricle. With the shift to the right, hypertrophy of the right cardiac chambers develops.

5. The reasons why one cannot demand the ideal picture relative to the location of the coronary arteries and the number of the cusps have

been stated. However, the surest landmark of the common trunk is the possession of four semilunar cusps, with two coronary arteries rising from the sinuses of opposite cusps, both shifted toward one of the interpolated cusps.

6. The crista supraventricularis proper (Spitzer) should stop at the base of the septum, beneath the ostium of the trunk.

7. The interatrial septum is defective according to the degree of detorsion at the venous end of the heart. There are varying degrees of patency of the foramen ovale (secundum), correlated with the degree of development of the limbus and the valve and with the displacement of the latter to the left. A foramen ovale primum may be present, or there may be complete absence of the atrial septum, both accompanied by a common atrioventricular opening.

8. The mitral and tricuspid leaflets undergo modifications of form and attachment, according to the degree of shift of the trunk to the right and the assumption by the trunk of the features of the "transposed" or "right" aorta.

There are no other recognized essential associated anomalies. A fairly common variant is the persistence of the right fourth aortic arch as the arch of the aorta, instead of the normal left.

CAUSE OF THE DEFECT

From a survey of the reported cases and a consideration of the developmental factors, it is obvious that the anomaly in question is frequently, if not invariably, associated with abnormal torsion. On theoretical grounds, one would expect to find septum formation impaired with a lag of torsion. So far as the evidence offered by the cases with four recognizable semilunar cusps goes, there is certainly a general parallelism between the degree of septum formation and the estimated torsion defect. That this parallelism is not absolute is indicated by the instances of "transposition" of the arterial trunk, with complete separation of the trunks, in spite of extreme detorsion. One must conclude that failure of development of the aortic-pulmonary septum, while almost invariably associated with detorsion, does not stand in a simple cause-effect relation to it.

From the evidence in my own case, it might be argued that the abnormality of the transection of the commissures instead of the lateral swellings by forerunners of the septum was responsible for the failure of descent. This certainly does not hold for the more numerous cases in which the indicated lines of descent were missing or were in the expected positions. Primary inequality of the fields belonging to the two trunks, perhaps associated with a missing bulb swelling, is probably

not a necessary factor. It seems likely that such inequality is responsible for some of the stenosed, often two-cusped trunks in "transposition."

There is no evidence in the anatomic structure of the lungs in the reported cases of any fundamental abnormality in the development of the pulmonary capillary bed. In these cases as in pulmonary atresia, more or less normal pulmonary function may develop, and even be maintained for years. In spite of Spitzer's theory that normal development of the pulmonary capiilary bed is an important element in the evolution of the septum, that structure may be absent or rudimentary in the presence of an adequate pulmonary circulation.

In the absence of any demonstrable correlation, one can only assume an intrinsic defect in the sixth arch system, with aplasia or early regression in the complete anomaly with only bronchial arteries, and with failure of normal growth, where sixth arch structures persist.

SUMMARY

There is much confusion regarding the criteria for identification of the common arterial trunk, and the literature shows many disagreements regarding the nature of the defect. The theories of the manner of development of the septums of the trunk and cardiac bulb are reviewed, as well as those pertaining to some of the defects commonly associated with imperfect development of these septums. These include abnormalities of torsion and the persistence of the reptilian right aorta (Spitzer).

The case reported is one of five in which the primitive trunk was readily identified by the possession of the theoretically required four semilunar cusps. The most widely accepted cases of persistent common trunk are reviewed. In addition to the five referred to, there are three in which the trunk had three cusps and a rudimentary fourth; five probable cases in which the trunk had three cusps, which satisfy many of the requirements, and seven cases in which the trunk had three cusps, which cannot be accurately classified. Of the thirteen probable cases, five are examples of the "partial" and eight of the "complete" defect. Five of the latter are the cases with three cusps of the third group above.

In only one case (one of the same group of five) did the patient survive to adult years. The other patients all died in infancy, although a number lived for several months. In general, the symptoms resembled those of pulmonic stenosis and atresia.

On the basis of the common features of the cases, and of theoretical considerations, suggested criteria for identification of the common arterial trunk have been evolved.

No satisfactory explanation of the cause of the anomaly has been found.

Of two cases recently reported as examples of persistent arterial trunk, that of Miller and Lyon (Am. Heart J. **7**:106, 1931) is an example of a single three-cusped trunk, with no recognizable derivatives of the sixth arches. Tow's case (Am. J. Dis. Child. **42**:1413, 1931) cannot be accurately classified from the information given.

Laboratory Methods and Technical Notes

REPORT ON NECROPSIES

PREPARED BY THE JOINT COMMITTEE REPRESENTING THE NEW YORK ACADEMY OF MEDICINE, THE NEW YORK PATHOLOGICAL SOCIETY AND THE METROPOLITAN FUNERAL DIRECTORS' ASSOCIATION

The joint committee began its work in 1930 and rendered a report on April 8, 1931, which was approved by the Council of the New York Academy of Medicine on May 27, 1931, and published in the *Bulletin of the New York Academy of Medicine* (**7**: 533, 1931). In accordance with the recommendation in section D, paragraph 3, of that report a continuing joint committee was designated to carry on the work of cooperation. Because of the unexpected large demand for copies of this original report the available reprints have become exhausted. The continuing committee therefore submits the present revision as a second report on necropsies, and recommends its adoption and printing in a periodical of wide circulation.

A. DESIRABILITY OF NECROPSY

1. All agree that postmortem examination by a pathologist is desirable; first, to provide reliable recorded information concerning the cause of death and the nature of the various disease processes; second, to confirm or amend the opinions formed by the physicians during the life of the patient, so that they may serve the next patient with greater confidence and skill; third, to reveal to the physicians continually the physical changes in the interior of the body which are associated with disordered behavior during life; fourth, to provide for the advance of human knowledge concerning the nature of disease in general. It is well recognized that the practice of postmortem examination in a hospital exercises a constant influence to improve the service and to correct serious deficiencies, as well as to improve diagnosis and prevent disease.

B. COOPERATION OF HOSPITAL AUTHORITIES AND FUNERAL DIRECTORS

1. The hospital and its medical staff have not completed their service to the family on the death of a patient. They owe to the family a further service, namely, to give an account of what has occurred, together with the most accurate possible explanation. This requires that some representative member of the family come to the hospital for a personal interview and give permission for the examination of the body of the deceased. The funeral director must recognize this relationship and should not oppose the proper efforts of the hospital authorities and the physicians in the discharge of this obligation.

2. The funeral director is particularly interested in getting into his own hands: (1) the death certificate, (2) the permit to remove the body

and (3) the body itself, so that he may prepare it in a satisfactory manner for the funeral ceremony. He must feel certain that nothing will arise to interfere with his plan and program. Unforeseen delay may require cancellation of contracts for transportation and various other services, thus increasing the expense and causing dissatisfaction. Unreasonable delay by the hospital, in its attempt to obtain permission for necropsy, is therefore objectionable to the funeral director. The conflict of interests in this connection requires mutual consideration and a spirit of cooperation on the part of all concerned. Disputes of this nature should therefore be adjudicated by a permanent joint committee on cooperation.

3. The funeral director or his agent must present to the hospital acceptable evidence that he has been authorized by the family to take charge of the body. The blank form employed for this purpose should conform with the requirements of the department of health.

4. Hospital employees, in general, must not give information to favored funeral directors or to any other unauthorized persons in regard to persons critically ill or dead in the hospital. It is proper for the chief administrative officer of the hospital, when requested by the family, to refer the selection of a funeral director to the office of the local Funeral Directors' Association, or, quite properly, to select one by rotation from an approved list in his own office. Such a selection must never be left to a minor employee of the hospital. Proof that a minor employee has offered recommendations of this sort should be followed by his instant dismissal from the service.

5. The hospital authorities should make certain that the necessary data for a death certificate, except those facts relating to the nature, progress and termination of the present illness, are entered on the record at the time of admission of the patient. Such data as date of birth and the maiden name of the mother may be obtainable only with great difficulty after death of the patient. The death certificate may be filled out by a clerk using a typewriter, leaving only the diagnosis and signature to be supplied by the physician who completes the certificate.

6. Report of a death to the medical examiner should be made in those circumstances where this is legally required, and the decision to notify this official should be made at the time of death of the patient, entirely without regard to the attitude of the relatives concerning necropsy. It is improper for any member of the hospital staff to threaten to call the medical examiner if permission for necropsy is refused. Any such procedure of threatening or browbeating may be regarded as evidence of lack of ability to handle the situation.

7. In general, the permission for necropsy should be asked for soon after the death has occurred. Often it is best to make the request at once whenever the proper relative of the deceased is present in the hospital. Reasonable consideration should be accorded to every one concerned in determining when the matter has been adequately presented and the final decision reached.

8. Arrangements should be worked out in every hospital whereby the unnecessary loss of time on the part of the funeral director may be

obviated, and the funeral director should be instructed that he will be promptly informed by telephone when the death certificate is signed and the body is ready for him.

The telephoned information in regard to the dead, particularly before a funeral director is known to have been engaged, should be given only by an executive officer of the hospital and should be carefully guarded unless the persons on the wire are personally known.

9. Interference by a funeral director with the legitimate efforts of the hospital to obtain permission for autopsy shall be regarded as a reportable grievance.

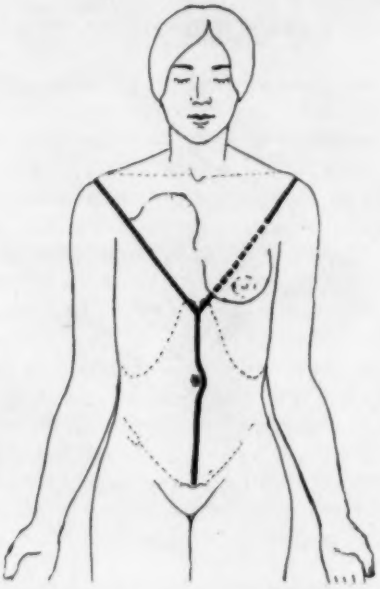

Fig. 1.—Diagram illustrating incisions in trunk.

C. TECHNIC OF THE NECROPSY

1. In males, the incision is to extend from the suprasternal notch to the pubes in the midline, passing to the left of the umbilicus. In no circumstances shall the incision in males be extended further upward.

2. In females and in sailors who are to be buried in uniform, the V-shaped incision is to be used, that is, an incision extending from the acromial end of the clavicle to the xiphoid and up to the acromial end of the corresponding clavicle. The flap thus outlined must be dissected upward close to the deeper structures, and every effort must be made to prevent perforation of the skin in the process of dissection.

3. At least from one-half to 1 inch (1.2 to 2.5 cm.) of the external carotid arteries is to be left free and ligated. The internal carotids and the vertebrals are to be ligated, and at least from one-half to 1 inch of the iliacs is to be left intact and ligated.

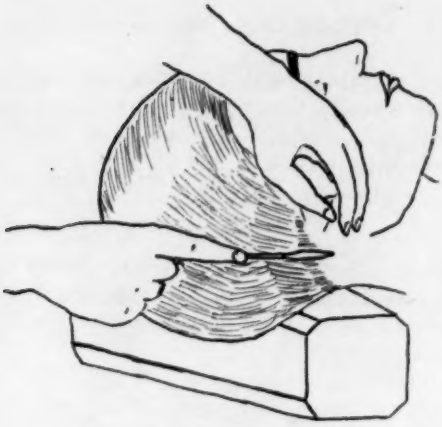

Fig. 2.—Incision in scalp.

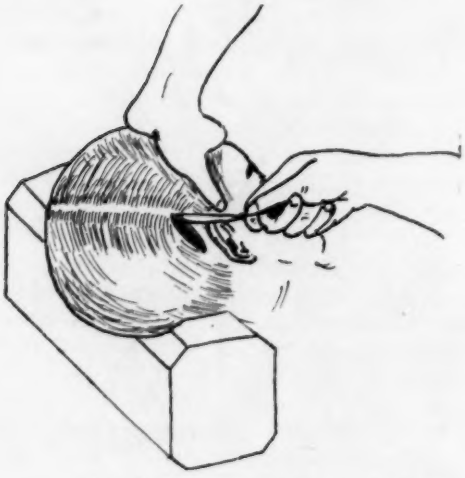

Fig. 3.—Incision in scalp.

Fig. 4.—Removal of skull cap.

4. The scalp is to be divided by an incision behind the ear, extending from one mastoid process to the other, as indicated in figures 2 and 3. The incision is to pass over the vertex when the hair is abundant, or somewhat posterior to this line when it is sparse. In women, the hair is to be parted along the projected line of incison to avoid cutting it. For the same reason, after the initial incision has been made, the knife should be carried in such manner that its sharp edge faces the dissector. Care should be taken not to tear or otherwise injure the scalp. The scalp is reflected backward and forward, so that the calvarium is exposed anteriorly slightly above the frontal eminences and posteriorly somewhat behind the occipital protuberance.

Before the skull is sawed, the line through which the saw is to be carried is to be mapped out with the aid of a sharp instrument (fig. 4). The temporal muscles are to be cut on a plane parallel with the projected line (fig. 4) to preserve stumps on either side long enough to provide for suturing and immobilization of the replaced calvarium.

5. The removal of the skull cap is to be planned and carried out in such a manner as to insure its secure approximation. This is best accomplished by sawing in two intersecting lines which meet at an obtuse angle behind the ear (fig. 3), the anterior incision commencing at the level of the hair line.

6. Before closing the cranial cavity, every effort should be made to provide against leakage. This is best carried out by the following procedures: (*a*) by ligating the carotid and vertebral arteries, (*b*) by plugging the foramen magnum tightly with cotton and (*c*) by filling the cranial cavity with oakum.

7. In suturing the skin a moderately small needle should be used so as to avoid leakage and disfigurement.

8. After the autopsy is completed, the body is to be delivered to the embalmer in a thoroughly clean condition—the skin washed, all cavities thoroughly sponged and dried and no source of leakage allowed to remain.

9. After the completion of the autopsy, the embalmer is to be allowed the use of the autopsy room for the preparation of the body for burial, provided that this does not conflict with the immediate use of the room for another autopsy and provided also that the embalmers leave no cleaning to be done by the hospital employees.

GEORGE BAEHR, M.D., *Chairman.*

General Review

CELLULAR REACTIONS OF TUBERCULOSIS AND THEIR RELATION TO IMMUNITY AND SENSITIZATION

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The problems concerning the pathogenesis of tuberculosis most discussed at the present time are inseparably associated with those of acute inflammation and immunity. The immediate local changes of the tissues in response to the tubercle bacillus resemble very closely the changes that follow other bacterial invasion and are identical with those that occur at the onset of inflammation produced by a great variety of irritants. The tubercle bacillus when first introduced causes scant exudation of fluid and active though transient emigration of polymorphonuclear leukocytes. The cell that later becomes predominant is a mononuclear phagocyte, which in anatomic and functional characters is similar to the mononuclear wandering cells that make their appearance whenever bacterial infection pursues a prolonged course and especially when it proceeds toward recovery. The problem of the origin of these cells is nearly half a century old, and whether they come from the blood or from the fixed tissues or from both is no better understood when their accumulation accompanies the healing of a pyogenic abscess than when as "epithelioid cells" they form the essential element of the tubercle.

The inflammatory reaction is profoundly influenced by the character of the tissue in which it occurs. The varying permeability of blood vessels in different parts of the body and the capacity of tissues to permit the accumulation of exudate are doubtless modifying factors. When a sterile irritant such as turpentine is injected into the subcutaneous tissue of a dog, an immense abscess with widespread destruction of tissue and accumulation of thick pus results, but when the same irritant in the same quantity is injected into the pleural cavity, there is a serofibrinous inflammation, which reaches maximum intensity at the end of three days and then subsides with complete restoration of the cavity to normal.

From the Henry Phipps Institute, University of Pennsylvania.

Similarly—but with due regard to peculiar characteristics of the tubercle bacillus as an inflammatory irritant—the nature of the reaction that follows its entry differs in different organs and tissues. When the disease implicates cavities that favor the accumulation of inflammatory exudates—for example, the pulmonary alveoli and the pleural, pericardial and meningeal cavities—the inflammatory nature of the reaction is generally admitted. Tuberculous pneumonia, universally recognized as a manifestation of tuberculosis only after the discovery of the tubercle bacillus, is a lesion predominately exudative and has characteristics that are reproduceable only in pulmonary tissue.

It is my belief that the use of the words exudative and productive, in the classification of tuberculous lesions, has introduced a confusion from which there is no escape save by eliminating them from nomenclature and using them only as descriptive terms. The tubercle, in accordance with the early conception of Baumgarten,[1] is formed, in part at least, by proliferation of cells at the site of its formation and hence has been regarded as productive. This opinion was based on the highly significant observation that the mononuclear cell that constitutes the chief cellular element of the tubercle multiplies by mitosis, but Baumgarten's deduction from this is no longer tenable. The cells and serum that accumulate in the alveoli of the lung with tuberculous pneumonia, on the contrary, are presumably exudative—that is, derived from the blood. This distinction can no longer be maintained since in the early stage of tubercle formation there is emigration of polymorphonuclear leukocytes, with other evidence of exudation from blood vessels. Moreover, mononuclear cells that accumulate in the alveoli also multiply by mitosis and assume the characteristics of those seen in the tubercle. Indeed, it is still uncertain whether the mononuclear wandering cells of tuberculous lesions are derived from wandering cells in the fixed tissue or from similar cells in the blood or from both blood cells and wandering cells of the tissues, and some still claim that they are derived from the endothelium of small blood vessels or lymphatics.

An intimate union between the fixed tissue of the affected part and the cellular elements that have accumulated under the stimulus of the tubercle bacillus is first obvious when reticular fibers, as Russakoff,[2] Snow Miller,[3] Foot[4] and others have shown, make their appearance. Snow Miller showed that there is no reticulum within the tubercle of the lung seven days after inoculation, whereas at the end of fourteen days, when epithelioid cells are abundant, there is a fine network of reticulum,

1. Baumgarten, P.: Ztschr. f. klin. Med. **9**:93, 1885; **10**:24, 1885.
2. Russakoff, A.: Beitr. z. path. Anat. u. z. allg. Path. **45**:476, 1909.
3. Miller, W. S.: Am. Rev. Tuberc. **7**:141, 1923; Am. J. Path. **3**:217, 1927.
4. Foot, N. C.: Am. J. Path. **1**:341, 1925.

which is coarser at the periphery of the tubercle, where it is continuous with the fibers of the adjacent normal alveolar walls. Later the tubercle is wholly permeated by reticular fibers. When collagen fibrils penetrate the tubercle and tend to replace it, they represent, Miller thinks, a continuation of the same process. These are reparative changes.

It is highly probable that the prolonged course of tuberculosis with formation of epithelioid and giant cells is attributable to the insoluble fat or wax that constitutes a considerable part of the tubercle bacillus and protects it from disintegration. There is a close but by no means exact resemblance between the tubercle and the reaction of the tissues to insoluble foreign bodies. Nevertheless, it is not improbable that differences in virulence such as that between the human and the bovine bacillus depend on factors other than the presence of insoluble fat (wax) and, resembling those that determine the virulence of other micro-organisms, are as yet unfortunately not well defined.

THE CELLULAR REACTIONS OF TUBERCULOSIS

Inflammation may be regarded as the process by which cells and serum accumulate about an injurious substance and as far as possible bring about its destruction or removal. The phenomena of inflammation repeat themselves in the same orderly succession with a great variety of bacteria, with many other micro-organisms and with various substances, either particulate or not, soluble or insoluble in body fluids, that act as sterile inflammatory irritants. The reaction is characterized by (1) exudation of fluid and emigration of polymorphonuclear leukocytes, followed, as this first stage decreases in intensity, by (2) accumulation of mononuclear phagocytes (macrophages). It has long been known that lymphocytes and monocytes (large mononuclear leukocytes) migrate from the blood vessels into the inflamed area, but what their relation is to one another and to the mononuclear phagocytes that are so abundant in the later stages of inflammation is a time-honored controversy.

I shall not discuss in detail the older literature describing the initial reaction of polymorphonuclear leukocytes to the tubercle bacillus. The studies of Benda [5] on the formation of tubercles in the glomerules of the human kidney show that it occurs in man as in other animals. Polymorphonuclear leukocytes are a conspicuous element in the tuberculous tissue formed when tubercle bacilli are injected into the pleural cavity of the dog, and leukoprotease is demonstrable in this tissue (Opie

5. Benda, C., in Pathologisch-anatomische Arbeiten Herrn Geh. Medicinalrath Dr. Johannes Orth zur Feier seines 25 jährigen Professoren—Jubiläums gewidmet, Berlin, A. Hirschwald, 1903, p. 520.

and Barker [6]). Lurie [7] found more polymorphonuclear leukocytes in rabbits after their infection with the bovine than after their infection with the human bacillus and more in the lung than in the liver; that is, they were more abundant with the more virulent strain and in the more susceptible organ.

The earliest stages in the formation of the tubercle were very recently described by Vorwald.[8] At the end of one hour after intravenous injection of tubercle bacilli, polymorphonuclear leukocytes form sharply localized collections in the alveolar capillaries. Even at this early period it is difficult to find tubercle bacilli that have not been taken up by polymorphonuclear leukocytes. By this means, the tubercle bacilli introduced into the blood stream are concentrated in small localized cellular masses, which are the ground-work for the development of tubercles. Accumulation of polymorphonuclear leukocytes is most conspicuous between the fourteenth and the eighteenth hour after inoculation. At this time, mononuclear cells are infiltrating the polymorphonuclear masses, ingesting the polymorphonuclear leukocytes and taking over the contained tubercle bacilli. After twenty-four hours, the focus of cells is predominantly mononuclear.

A second less active migration of polymorphonuclear leukocytes occurring when the tubercle undergoes caseation has been described by Kostenetsch and Wolkow [9] and subsequent observers. It is evident that polymorphonuclear leukocytes that penetrate into the caseous material may undergo destruction. Medlar [10] found evidence that polymorphonuclear leukocytes induce caseation. The pathogenesis of a tuberculous cavity is, however, very different from that of an abscess, and Medlar's designation of a tuberculous cavity as an abscess is not, I believe, well chosen.

The notable observation of Baumgarten [1] that the mononuclear cell that constitutes the chief element of the tubercle undergoes active mitotic division was accepted by many as evidence that the epithelioid cell is derived from fixed cells of the part affected. Increased knowledge of the wandering cells of the blood and of the tissues has modified this opinion, but has not diminished the significance of the observation, which is often forgotten.

The epithelioid cells of the tubercle have a superficial resemblance to true epithelial cells, because there is no appreciable intercellular substance between them. They have distinctive cytologic characteristics.

6. Opie, E. L., and Barker, B. J.: J. Exper. Med. **10**:645, 1908.
7. Lurie, M. B.: J. Exper. Med. **55**:31, 1932.
8. Vorwald, A. J.: Am. Rev. Tuberc. **25**:74, 1932.
9. Kostenetsch and Wolkow: Arch. de méd. expér. et d'anat. path. **4**:741, 1892.
10. Medlar, E. M.: Am. J. Path. **2**:275, 1926.

They are large cells, and each has a large nucleus and, as Castrén [11] observed, a well developed cytocentrum and a large attraction sphere.

The characteristics of the epithelioid cell of the tubercle after supravital staining with neutral red and the central rosette of neutral red granules were first described by Sabin, Doan and Cunningham [12] and subsequently by M. R. Lewis, Willis and W. H. Lewis [13] and others. Neutral red granules form a rosette near the center of the cell with the nucleus just outside it. The granules are radially arranged about a clear central spot in which is the centrosome of the cell. The cytoplasm surrounding the neutral red rosette contains a varying number of fat globules, mitochondria and possibly other granules. A thin, clear peripheral zone is often extended out into short, irregular membranous pseudopodia. Giant cells similarly stained have precisely the same structure, with the nuclei arranged about a central group of neutral red granules.

Sabin, Doan and Cunningham found that some of the wandering cells of the connective tissue and of the tubercle possess a neutral red rosette like that of the monocyte of the blood, whereas others exhibit neutral red granules scattered through the cell. Carrel and Eberling [14] by tissue culture methods found that the distribution of neutral red granules in the mononuclear wandering cell is dependent on the functional activity of the cell, and Lewis and Lewis [15] found that monocytes of the blood in tissue culture produced cells with scattered neutral red granules. The opinion that variations of supravital staining identify functional phases of one type of cell seems to be widely accepted.

The evidence at hand indicates that monocytes and epithelioid cells, both with neutral red rosettes, increase in number with tubercle formation. Mononuclear phagocytes with scattered neutral red granules are constantly present in considerable number. It is not yet evident what the relation of one to the other is as they occur in the tubercle.

Sabin, Doan and Forkner [16] found that phagocytes with diffusely scattered neutral red granules ingest and fragment tubercle bacilli, and maintained that the micro-organism persists intact in the monocyte. On the other hand, disintegration of tubercle bacilli within monocytes of

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11. Castrén, H.: Arb. a. d. path. Inst. zu Helsingfors **3**:191, 1925.

12. Sabin, F. R.; Doan, C. A., and Cunningham, R. S.: Contrib. Embryol. **16**: 125, 1925.

13. Lewis, M. R.; Willis, H. S., and Lewis, W. H.: Bull. Johns Hopkins Hosp. **36**:175, 1925.

14. Carrel, A., and Eberling, A. H.: J. Exper. Med. **44**:285, 1926.

15. Lewis, M. R., and Lewis, W. H.: Contrib. Embryol. **18**:95, 1926.

16. Sabin, F. R., and Doan, C. A.: J. Exper. Med. **46**:627, 1927. Sabin, F. R.; Doan, C. A., and Forkner, C. E.: ibid. (supp. no. 3) **52**:1, 1930.

the guinea-pig is described by Gottlieb [17] and in epithelioid cells of the rabbit by Lurie.[7] The destruction of tubercle bacilli by epithelioid cells will be discussed later.

In the absence of knowledge concerning the behavior of the neutral red rosette of the mononuclear phagocyte in the presence of various particulate and other chemical irritants in varying quantitative relations, it is doubtful if it can be successfully used as a criterion for analysis of the chemical constituents of the tubercle bacillus. It is difficult, for example, to interpret the significance of cellular reactions obtained by intraperitoneal injection of quantities of phospholipin equivalent to the content of 5 Gm. of tubercle bacilli (Sabin and Doan).

The experiments of Lurie [7] working at the Henry Phipps Institute have shown that different organs possess inherently different power to destroy tubercle bacilli before the phenomena of immunity or of sensitization have made their appearance. He counted the number of colonies obtainable from a weighed quantity of tissue, and found that when tubercle bacilli are injected into the blood stream of the rabbit, they, like inanimate particulate matter such as carbon particles, lodge in greatest number in the spleen, in somewhat smaller absolute numbers in the liver, though in relatively larger numbers in proportion to its volume, and in diminishing numbers in the lungs, bone marrow and kidneys. In all of these organs, tubercle bacilli multiply for several weeks. Human tubercle bacilli multiply more rapidly than bovine bacilli. With human tubercle bacilli, which are relatively avirulent for rabbits, multiplication ceases between the second and the fourth week, and with small doses, somewhat later (from the fourth to the eighth week). Subsequently the number of tubercle bacilli rapidly diminishes in all of the organs that have been named, but much more slowly in the lung, where multiplication was greatest.

With bovine tubercle bacilli, which are virulent for rabbits, as with the human micro-organisms, there is at first some but less multiplication in the spleen, liver and bone marrow, followed by progressive destruction beginning after the fourth week and completed after two months. The fate of the virulent bovine tubercle bacilli in the lung and kidney is wholly different from that of the human bacilli, since multiplication proceeds uninterruptedly and is the evident cause of death. A comparison between these changes indicating the fate of the tubercle bacilli and the histologic changes in the tissue has given new insight into the significance of the reaction that produces the tubercle. When human tubercle bacilli or bovine bacilli of an avirulent strain are injected intravenously, mononuclear wandering cells accumulate in the alveolar septums of the lung in appreciable numbers to form small groups

17. Gottlieb, R.: Am. Rev. Tuberc. **25**:172, 1932.

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16. Sabin, F. R., and Doan, C. A.: J. Exper. Med. **46**:627, 1927. Sabin, F. R.; Doan, C. A., and Forkner, C. E.: ibid. (supp. no. 3) **52**:1, 1930.

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17. Gottlieb, R.: Am. Rev. Tuberc. **25**:172, 1932.

within twenty-four hours. In an early tubercle of the lungs, at the end of a week, when tubercle bacilli are multiplying, these cells have taken on the characteristics of young epithelioid cells, the center of the nodule being composed of larger cells, each with reticulated cytoplasm and a large, round nucleus poor in chromatin. At the periphery there is a closely packed ring of smaller mononuclear cells, many of which are undergoing mitotic division. There are numerous tubercle bacilli in the young epithelioid cells. The presence of acid-fast granules in these cells indicates that tubercle bacilli are in process of destruction. At the end of two weeks, when the number of tubercle bacilli demonstrable by cultures has diminished, the epithelioid cells have assumed a more mature character and the surrounding ring of smaller mononuclear cells is very thin or absent.

While the tubercle bacilli are multiplying, young mononuclear wandering cells at the periphery of the tubercle are multiplying by mitosis to form epithelioid cells that ingest and destroy the bacilli; when the invading bacilli have been destroyed, mitosis ceases, giant cells appear, and subsequently lymphocytes and fibroblasts invade the tubercle.

It is noteworthy that mononuclear phagocytes that accumulate within the interstitial tissue of the lung and form tubercles evidently destroy the tubercle bacilli much more effectively than the similar cells that have accumulated within the alveoli. Here there may be numerous tubercle bacilli within cells with the characteristics of epithelioid cells at a time when they have disappeared from interstitial tubercles.

After intravenous injection of bovine tubercle bacilli, their multiplication in the lung, measured by cultural methods, proceeds uninterruptedly. The initial cellular reaction is more intense, the migration of polymorphonuclear leukocytes and the accumulation of mononuclear cells being much more active than after injection of the less virulent human tubercle bacilli. In interstitial tubercles, the micro-organisms are held in check, and few are found in epithelioid cells, but the pneumonic process proceeds unrestrained. Tubercle bacilli are numerous, the lesion is widespread, and caseation is extensive; new formation of epithelioid cells continues unabated to the end, and giant cell formation is inconspicuous.

Enumeration of colonies shows that tubercle bacilli disappear more readily in the liver, spleen and bone marrow than in the lungs, and histologic examination shows that acid-fast particles formed by disintegration of tubercle bacilli quickly make their appearance in the Kupffer cells of the liver, in the macrophages of the spleen and in the reticular cells of the bone marrow. The mononuclear wandering cells of different organs evidently vary in their capacity to destroy tubercle bacilli. With human tubercle bacilli, this destruction in the liver is occurring between the second and the fourth week, at a time when

mononuclear cells are multiplying by mitosis and assuming the characteristics of mature epithelioid cells. With bovine bacilli, the same process occurs somewhat later. With prompt destruction of tubercle bacilli in the liver, the whole process pursues a much more rapid course than in the lung; numerous small tubercles are formed, giant cells appear early, and caseation is inconspicuous. Between the sixth and eighth weeks, only a few bacilli are demonstrable by cultures, and tubercles of the liver, unlike those of the lung, have disappeared.

In the spleen there was histologic evidence that destruction of tubercle bacilli progressed more rapidly in the pulp than in the corpuscle, accumulation of acid-fast particles being more conspicuous in the mononuclear phagocytes of the former. Tubercle bacilli disappeared sooner, mitosis was less conspicuous, and giant cells appeared earlier in the tubercles of the pulp. In the corpuscle, mitosis of mononuclear cells persisted longer, and tubercles attained a much larger size and were present at a time when they had disappeared from the pulp.

During the period when tubercle bacilli are multiplying and accumulating within the mononuclear cells there is proliferation of these cells by mitosis, and the more active the growth of the bacilli the greater the regeneration of the cells. Mitosis is more conspicuous in the lung, which destroys the micro-organism slowly, than in the liver, in which destruction is rapid. At the time when tubercles consist of mature epithelioid cells, tubercle bacilli have already been in great part destroyed.

Summary.—It is now possible to formulate a somewhat more exact conception of the development of the tubercle. The mononuclear cells that first accumulate mature to form epithelioid cells. At their periphery new mononuclears are formed, in part at least, by mitotic division, and these in turn mature to form epithelioid cells. This process continues from the periphery inward as long as living tubercle bacilli persist. Caseation occurs in the center of the tubercle, and an increasing number of epithelioid cells may be involved. The fatty droplets in these cells are doubtless evidence of beginning degeneration.

The most important factor in the destruction of the tubercle bacillus is the young epithelioid cell, but available evidence suggests that the polymorphonuclear leukocyte has a part in preparing the way for it.

CELLULAR REACTIONS OF REINFECTION WITH TUBERCULOSIS

It would be unprofitable to review in detail observations concerning the cellular changes on reinfection by the tubercle bacillus. Significant observations, not widely known, were made by Joseph Nichols.[18] Rabbits were first infected with avirulent and later with virulent human

18. Nichols, J. L.: M. News **87**:638, 1905.

tubercle bacilli. During the first three or four days these animals exhibited a higher temperature than controls infected for the first time with the virulent bacilli and were apparently sick. Subsequently this relation was reversed, the reinfected animals returning to normal when the controls began to decline. In the reinfected animals during the period of illness, tubercles composed of epithelioid cells appeared with much greater rapidity than in the controls; giant cells appeared as early as the third day; tubercle bacilli soon disappeared; there was no caseation, and the lesion in large part underwent resolution. In the controls, on the contrary, tubercles were formed slowly and gradually; they increased in size; tubercle bacilli persisted; caseation occurred, and giant cells did not appear until the twenty-fifth day.

By enumeration of colonies in suitably prepared cultures, Lurie [19] followed the fate of tubercle bacilli injected into the venous system in rabbits previously infected with tuberculosis. On reinfection with either human or bovine bacilli there was no primary multiplication in the organs such as occurred with the first infection, but destruction of bacilli began immediately after injection and proceeded far more rapidly than in the uninfected animals. This relation was very obvious in the liver, spleen and bone marrow, though determined with greater difficulty in the lung and kidney, because tubercles of the first infection persisted in considerable numbers in these organs. Scant, if any, macroscopic tuberculosis referable to the new infection made its appearance, and microscopic examination showed that an active, ephemeral accumulation of polymorphonuclear leukocytes was followed by a rapid nodular accumulation of mononuclear cells (observations in process of publication). Coincident with the disappearance of tubercle bacilli as determined by cultures, these cells matured to form epithelioid and giant cells within one week after inoculation. Young mononuclear cells undergoing mitosis were present in scant number and soon disappeared. Within two weeks in the liver and spleen and within four weeks in the lungs, the new tubercles had largely disintegrated, and after this time were rarely found.

The foregoing statements apply to rabbits in which the lesions of first infection persisted in the lungs and kidneys. When the primary lesions had almost completely disappeared, the ability of the animals to control a second infection was somewhat diminished and expressed itself by a less accelerated inflammatory reaction. The course of reinfection with human bacilli was the same, but after reinfection with bovine bacilli there were occasionally slight tuberculous lesions, far less extensive than the massive tuberculosis of first infection.

19. Lurie, M. B.: J. Exper. Med. **50**:747, 1929.

Summary.—In animals reinfected with tubercle bacilli, the initial transient accumulation of polymorphonuclear leukocytes and the subsequent formation of epithelioid and giant cells proceed more promptly and with greater intensity than in previously uninfected animals.

Tubercle bacilli are destroyed with greater rapidity in the epithelioid cells of the reinfected animals.

After destruction of the tubercle bacilli in the tuberculous lesions of the reinfected animals, the lesions may undergo partial or complete resolution.

LOCAL FIXATION OF TUBERCLE BACILLI WITH REINFECTION

The changes at the site of reinfection were compared with those at the site of first infection by Lewandowsky,[20] who introduced tubercle bacilli by scarification of the skin surface. Twenty-four hours after the second infection there was intense inflammatory edema, and leukocytes had accumulated in great numbers about the tubercle bacilli, which were present in conspicuous clumps. Necrosis of tissue had occurred about them, and polymorphonuclear leukocytes near the micro-organisms had undergone destruction. Between the fourth and the seventh day after inoculation, the necrotic tissue, carrying with it the greater part of the infecting tubercle bacilli, had been cast off, leaving an ulcerated surface; in the edges of the defect at the end of a week there were epithelioid and some giant cells, but few or no tubercle bacilli. In animals with a first infection there was fairly intense infiltration with epithelioid cells and giant cells, and tubercle bacilli were present in considerable numbers. Lewandowsky thought that the necrosis and sloughing of the dead tissue at the beginning of reinfection eliminated the greater part of the inoculated tubercle bacilli.

In this connection, the observations of Krause and Willis[21] on the local fixation of tubercle bacilli at the site of reinfection are significant. By inoculation of excised tissue into guinea-pigs they showed that dissemination of tubercle bacilli injected into the skin of previously infected guinea-pigs proceeds much more slowly than in guinea-pigs infected for the first time. In animals rendered both sensitive and resistant by foregoing infection, transit of bacilli from the site of entry to neighboring lymph nodes, a distance of 4 or 5 cm., required two or three weeks, whereas in previously uninfected animals it was made within twenty-four hours. They cited the local fixation of bacteria at the site of an inflammatory reaction, and believed that retardation of dissemination is the result of the heightened inflammatory reaction that

20. Lewandowsky, F.: Arch. f. Dermat. u. Syph. **123**:1, 1916.

21. Krause, A. K.: Am. Rev. Tuberc. **11**:343, 1925. Willis, H. S.: ibid., p. 427.

occurs in the sensitized animal. My associate, Dr. Freund, using dead tubercle bacilli to protect guinea-pigs, obtained similar results.

This retardation of spread, Rich [22] suggested, may be attributable to a destruction of the bacilli referable to immunization, but he said that the heightened inflammatory reaction doubtless promotes the accumulation of cellular elements and serum containing antibodies at the site of invasion and destroys rather than fixes the bacilli. My observations [23] on the pathogenesis of Arthus' phenomenon, which has only partial resemblance to the inflammatory reaction occurring at the site of reinfection with tubercle bacilli, show that the foreign protein injected into the skin of an immunized animal is fixed at the site of entry and fails to reach the blood stream, whereas in a normal animal it produces scant inflammatory reaction and readily finds its way into the blood.

Pyogenic bacteria injected into the peritoneal cavity previously inflamed by an irritant do not enter the blood stream, whereas when bacteria and the irritant are introduced simultaneously, dissemination of the former is not prevented. When the fate of the tubercle bacilli introduced into the skin of an animal into which such bacilli have previously been injected is compared with the dissemination of bacteria introduced at the site of a sterile inflammatory reaction, it is significant that the tubercle bacilli themselves, like the foreign protein mentioned, incite the inflammation, evidently with the aid of some factor produced by an antigenic reaction. Antibodies, such as precipitins or agglutinins, may have a part in the local fixation of foreign protein or bacteria.

Summary.—The available evidence indicates that the heightened inflammatory reaction of animals sensitized by infection with tubercle bacilli promotes the local fixation of reinfecting micro-organisms.

CASEATION AND SENSITIZATION

The relation of caseation to sensitization, or allergy, has been much discussed. It is doubtful if any useful analogy can be found between the necrosis produced by cutaneous reinfection of a tuberculous animal (Koch's phenomenon), or the necrosis caused by tuberculin introduced into the skin of a tuberculous animal, and the caseation that affects tuberculous lesions. It is certainly true that more information about each one of these processes must be obtained before one can be satisfactorily compared with another. The local necrosis produced by the injection of tubercle bacilli into the skin of a tuberculous animal is accompanied by an acute inflammatory reaction and has little resemblance to the necrosis that affects lesions composed in considerable part

22. Rich, A. R.: Bull. Johns Hopkins Hosp. **47**:189, 1930.
23. Opie, E. L.: J. Exper. Med. **39**:659, 1924.

of epithelioid cells. These cells, when they have reached maturity, already show degenerative changes. Some writers assume that the number of tubercle bacilli found in association with tuberculous lesions may be too small to explain the occurrence of massive caseation unless the tissue is hypersusceptible to the action of products of the micro-organism. In the absence of any method by which these relations can be measured, speculation is unprofitable. It is noteworthy, on the other hand, that the tuberculous lesions produced in animals that have previously been infected with tubercle bacilli and are in consequence highly sensitive to tuberculin as demonstrated by skin tests, may exhibit much less caseation than those of control animals infected for the first time. This relation has been observed by Dr. Freund and myself in rabbits that had received repeated injections of dead tubercle bacilli and had thus been rendered both sensitive to reinoculation and resistant to living tubercle bacilli. My associate, Dr. Aronson, infected guinea-pigs with B C G and subsequently inoculated them with virulent human tubercle bacilli. Just before these animals were killed, six weeks after the second inoculation, they reacted strongly to tuberculin. There were a few tubercles in abdominal organs, notably in the spleen; in the lungs and tracheobronchial lymph nodes there were large, firm, gray foci of tuberculosis with scant spots of caseation. In control animals with a first infection there was tuberculosis with massive caseation in the spleen, lungs and tracheobronchial lymph nodes. In reinfected animals, tubercle bacilli had resisted destruction in sufficient number to produce extensive lesions, but sensitization had produced little, if any, caseation. In Lurie's experiments, on the contrary, with tubercle bacilli virulent enough to multiply in previously uninfected or in reinfected animals, new formation of epithelioid cells proceeded uninterruptedly, and caseation was extensive.

The significant experiments of Rich and Lewis [24] in vitro show that cells of the tuberculous animal are peculiarly susceptible to injury by tuberculin. In the living animal, caseation is most likely to occur where epithelioid cells are numerous. Multiplication of tubercle bacilli with continued new formation of epithelioid cells is probably the most important factor in caseation. Under these conditions, sensitization may hasten caseation, but it may perhaps occur with no sensitization.

Summary.—It is by no means improbable that the extent of caseation is influenced by sensitization to products of the tubercle bacillus, but since coexisting resistance to the micro-organism or its products may at the same time hold caseation in check, definite knowledge concerning the relation of caseation to sensitization must doubtless wait for improved experimental methods.

24. Rich, A. R., and Lewis, M. R.: Bull. Johns Hopkins Hosp. **50**:115, 1932.

Multiplication of tubercle bacilli, stimulating the new formation and maturation of epithelioid cells, is probably more important in the production of caseation than is sensitization.

SENSITIZATION AND RESISTANCE (ALLERGY AND IMMUNITY) WITH TUBERCULOSIS

Koch's description [25] of the cutaneous reaction to reinfection expresses the greater part of what is known today concerning the relation of sensitization to immunity in tuberculosis. In a guinea-pig infected with tuberculosis for the first time by injection into the skin, the cutaneous lesion appears slowly and persists until death, but in a previously infected animal an intense inflammatory reaction associated with superficial necrosis produces an ulcer that quickly heals without infection of the neighboring lymph nodes.

It is evident why some of those who repeated Koch's experiment failed to obtain the same result. Kalbfleisch [26] did not find the reaction any more intense in rabbits that had previously been given a small infecting dose of tubercle bacilli than in normal animals, but in animals that had been given injections of larger quantities Koch's phenomenon was readily reproduced. In agreement with this observation, Roemer and Joseph [27] had found that a feeble tuberculin reaction was obtained in guinea-pigs a month and a half after their inoculation with small quantities of tubercle bacilli, but that after their inoculation with larger quantities a more intense reaction appeared within twenty-three days.

Sensitization as related to the tubercle bacillus is measurable (1) by reinoculation of living tubercle bacilli (Koch phenomenon), (2) by tests with tubercle bacilli killed by a variety of agents, (3) by tests with extracts obtained by methods that preserve intact the protein contents of the tubercle bacillus and (4) by tests with extracts in which the protein and doubtless other constituents of the micro-organism are profoundly modified. The best example of the latter is old tuberculin, which in preparation is subjected to prolonged heat at boiling temperature.

Information concerning sensitization obtained by one of these methods is not transferable to another. Tuberculoprotein, like other foreign protein, as Baldwin [28] and others have found, acts as an antigen, sensitizes to anaphylactic shock and, as its recent use in relatively large doses has shown, causes "anaphylactic" inflammation similar to that produced by other foreign protein in a sensitized animal (Arthus' phenomenon). Old tuberculin, on the contrary, is not an

25. Koch, R.: Deutsche med. Wchnschr. **17**:101, 1891.
26. Kalbfleisch, H. H.: Beitr. z. Klin. d. Tuberk. **70**:465, 1928.
27. Roemer, P. H., and Joseph, K.: Beitr. z. Klin. d. Tuberk. **14**:1, 1909.
28. Baldwin, E. R.: J. M. Research **22**:189, 1910.

antigen in the usual sense, but serves to manifest reactions that it cannot incite.

Rich [29] stated that tuberculous animals desensitized by repeated injections of tuberculin are still resistant to a new infection with tubercle bacilli. Aronson, however, has found, he informs me, that tuberculous animals desensitized to tuberculin still exhibit the Koch phenomenon. Such experiments involve quantitative relations that must be more fully investigated. Existing criteria of sensitization are necessarily vague.

In the attempt to define the relation between sensitization and immunity to tuberculosis, the difficulties of measuring immunity are equally great. The criteria available are resistance to reinfection (always relative, and experimentally determined by prolongation of life or by percentage of recovery) and formation of antibodies, which may have little if any obvious relation to protection against this disease. Sensitization is a phenomenon readily demonstrable in association with some infectious diseases and inconspicuous if it occurs with others. There is no evidence to indicate that it is essential to protection. Experiments directed to the protection of cattle with the bovovaccine of von Behring showed that the tuberculin reaction and protection against reinoculation were lost after a year or a year and a half, and there is a good deal of evidence that human beings lose their susceptibility to tuberculin with complete recovery from infection. With reinfection, the formation of antibodies occurs more rapidly than after first infection,[30] and there is some evidence that the tuberculin reaction in human beings lost after first infection reappears with unusual rapidity after reinfection. These observations vaguely suggest that there are factors involved in immunity against tuberculosis independent of sensitization and of the formation of antibodies and even of the usual manifestation of resistance.

Summary.—Sensitization is inseparably associated with immunity, but since each is dependent on factors peculiar to itself, they do not necessarily proceed parallel.

RELATION OF SENSITIZATION (ALLERGY) TO HUMAN TUBERCULOSIS

The evident symptoms and profound injury to tissue that are produced in sensitive animals by products of tubercle bacilli support the assumption that hypersusceptibility to these products plays an important part in the symptomatology and pathogenesis of human tuberculosis.

29. Rich, A. R.: Proc. Nat. Acad. Sc. **16**:460, 1930.

30. Mudd, S.; Lucké, B.; McCutcheon, M., and Strumia, M.: J. Exper. Med. **49**:779, 1929. McCutcheon, M.; Strumia, M., and Mudd, S.: ibid., p. 797. McCutcheon, M., and others: ibid., p. 815.

The number of publications in which this fascinating subject is discussed is very great, especially in Germany, where interest in it has been stimulated by the important anatomic observations and highly speculative writings of Ranke.[31] Unfortunately there is little agreement on what may be regarded as evidence of sensitization, or allergy.

Three stages in the development of human tuberculosis, according to Ranke, are comparable with those of syphilis. The first change following the lodgment of the tubercle bacillus in the lung is, he said, a pneumonic process, and the first histologic evidence of altered reaction is tubercle formation. The second stage of infection, characterized by heightened susceptibility, is associated with dissemination of the infection by the blood stream. The third stage, or stage of immunity, is best illustrated by slowly progressive pulmonary tuberculosis, with which spread is chiefly by way of tubular channels, such as the bronchi.

Few pathologists accept the opinion that tuberculosis acquired in childhood progresses through the stages described by Ranke, but among those who regard the phthisis of adults as a reinfection acquired by those infected in childhood, opinions concerning the significance of sensitization differ widely. Aschoff,[32] like Ranke, regards the dissemination of tuberculosis in childhood as an anaphylactic phenomenon accompanied by exudation and rapid caseation affecting lymph nodes especially. Others, including myself, believe that dissemination by way of the lymphatic system and blood stream is the usual manifestation of tuberculous infection in susceptible animals unprotected by a previous infection. Tuberculosis of reinfected animals and the usual pulmonary tuberculosis of adult human beings are characterized by scant, if any, caseation of adjacent lymph nodes and are rarely accompanied by blood stream dissemination (Ranke, Opie,[33] Aschoff,[34] Schurmann[35]).

Those who have studied the primary deposition of tubercle bacilli in the tissues agree that the first changes are inflammatory. Prudden[36] produced massive caseous pneumonia by injecting tubercle bacilli into the bronchi of rabbits. Bezançon and di Serbonnes[37] found that the first effect of the introduction of tubercle bacilli into the lung of a normal guinea-pig by way of the trachea is an alveolitis with congestion of blood vessels and accumulation of mononuclear cells with some

31. Ranke, K. E.: Deutsches Arch. f. klin. Med. **119**:201 and 297, 1916; **129**: 224, 1919.

32. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924, p. 34.

33. Opie, E. L.: J. Exper. Med. **25**:855, 1917; **26**:263, 1917.

34. Aschoff, L.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **33**:13, 1921.

35. Schurmann, P.: Beitr. z. klin. Med. **68**:723, 1928.

36. Prudden, M.: New York M. J. **60**:1, 1894.

37. Bezançon, F., and di Serbonnes: Ann. de méd. **1**:149, 1914.

polymorphonuclear leukocytes, followed by caseation. When tubercle bacilli were introduced into the tracheas of guinea-pigs shown by skin tests to be sensitized by previous infection, there was alveolar inflammation, but no caseation, and the lesion soon assumed the character of chronic interstitial pneumonia.

Summary.—Experimental evidence shows that sensitization to products of the tubercle bacillus modifies the character of tuberculous lesions and increases the intensity of the inflammatory reaction to the tubercle bacillus, but there is as yet scant information by which the varying character of human lesions can be more exactly interpreted as manifestations of sensitization.

The assertion frequently made that frank tuberculous pneumonia is never the result of a first infection is, I believe, incorrect. It is not improbable that the extent of a tuberculous pneumonia may be increased by sensitization of the tissues, but experimental and human evidence indicates that massive caseous pneumonia is more likely to occur in the absence of previous infection.

The apical tuberculosis of adults has the characteristics of tuberculosis in animals made resistant by previous infection. It usually pursues a chronic course, remains localized in the lung and is unaccompanied by caseation of adjacent lymph nodes.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—T. D. Beckwith has been appointed associate professor of bacteriology in the University of California at Los Angeles.

Martin Frobisher has been appointed associate in epidemiology in the Johns Hopkins School of Hygiene and Public Health, Baltimore.

In the school of medicine of the University of Texas at Galveston, Wendell Gingrich has been appointed professor of bacteriology and preventive medicine, and William M. Powell instructor in pathology.

Lyman L. Daines, professor of pathology and bacteriology in the school of medicine of the University of Utah, has assumed the deanship of the school.

Maurice Nicolle, bacteriologist and professor in the Pasteur Institute in Paris, has died at the age of 70.

In the medical college of Cornell University in New York, James Ewing is professor of oncology; Lawrence W. Smith, assistant professor of pathology, and Fred W. Stewart, Jacob Furth and Jules Freund, associates in pathology.

Society News.—The American Association of Pathologists and Bacteriologists will meet in Washington, D. C., on May 9 and 10, 1933, in conjunction with the Congress of American Physicians and Surgeons.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

LOCALIZATION OF EXPERIMENTAL VENTRICULAR MYOCARDIAL LESIONS BY THE ELECTROCARDIOGRAM. J. H. CRAWFORD, G. H. ROBERTS, D. I. ABRAMSON and J. C. CARDWELL, Am. Heart J. **7**:627, 1932.

Electrocardiographic changes were studied in relation to the site of damage in thirty-four cats in which localized ventricular myocardial lesions had been produced by the electric cautery. Curves of monophasic type were obtained, which were classified as of the T_1 and T_3 types of Parkinson and Bedford. With almost complete consistency, lesions in similar sites produced the same type of curve. Lesions on the anterior surface of the left ventricle produced curves of the T_1 type, while those on the posterior surface of the left ventricle, including the apex, yielded the T_3 type. All right ventricular sites, except the base anterior, in which only a slight change was induced, gave curves of the T_3 type. At the apex posterior alone were the changes comparable in magnitude with those obtained in the left ventricle. Usually the changes produced were marked in two leads. In some the displacement of the R-T segment was oppositely directed in the remaining lead, while in others no significant deviation was observed in this lead. In a few instances, an R-T elevation was present in all three leads, but as a rule to a greater extent in one lead. In three experiments, in each of which the lesion was located at the base anterior, depression rather than elevation of the R-T segment occurred.

AUTHORS' SUMMARY.

EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM AND OSTEITIS FIBROSA IN PUPPIES. JOSEPH L. JOHNSON, Am. J. M. Sc. **183**:761 and 769, 1932.

Parathormone in doses of from 10 to 20 units was injected daily for periods of from ten to forty-three days into white rats, aged from 6 to 12 weeks. The rats were fed the Steenbock diet for normal rats. Control litter mates remained well, whereas the animals given parathormone, without exception, showed muscular weakness, hypotonia and skeletal lesions characteristic of osteitis fibrosa osteoplastica (von Recklinghausen), namely, a lacunar resorption of bone with softening and deformity, bending and multiple fractures. In the affected bones, the cortex and marrow were largely replaced by fibrous connective tissue containing numerous giant cells, and new osteoid tissue was also in evidence in numerous cases. Chronic hyperparathyroidism produced in rats by repeated injections of parathormone leads to bone changes that justify a diagnosis of osteitis fibrosa. These experiments support the conclusion that the cause of clinical osteitis fibrosa osteoplastica (von Recklinghausen) is an excess of the parathyroid hormone.

The experimental production in puppies of a state of chronic hyperparathyroidism is reported, and descriptions are given of the gross, roentgenologic and microscopic abnormalities resulting therefrom. This experimental disease, produced with repeated injections of parathormone, is characterized by skeletal lesions and other abnormalities which correspond closely to those observed in clinical cases of osteitis fibrosa osteoplastica.

AUTHOR'S SUMMARIES.

EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM AND EFFECTS OF IRRADIATED ERGOSTEROL. JOSEPH L. JOHNSON, Am. J. M. Sc. **183**:776, 1932.

An answer was sought to the question as to the relationship of osteitis fibrosa to those other skeletal diseases, especially rickets and osteomalacia, that are also

associated with hypertrophy of parathyroid glands. Metabolic studies of the problem have been reported; the results of animal experiments are given here. Viosterol, in a dosage of from 5 to 60 drops daily, was fed to young, white rats and puppies maintained in a chronic state of hyperparathyroidism by the daily injection of parathormone. These animals were litter mates of others that developed the skeletal lesions of osteitis fibrosa when treated with parathormone alone. The technic of experimentation, the diets and the dosage of the parathormone were the same as previously reported. The outcome was the same, except that the resulting lesions typical of the skeletal abnormalities of osteitis fibrosa were, on the whole, more extensive. Metastatic calcification in the kidneys was also more marked. Whereas vitamin D concentrates effectively protect against rickets or osteomalacia, it is evident from these experiments that they intensify the disease produced by excess of parathyroid hormone. It is therefore clear that rickets and osteomalacia differ essentially in pathogenesis from osteitis fibrosa. While the hypertrophy of the parathyroid glands in conditions of vitamin D deficiency may be compensatory and is certainly a secondary phenomenon, the tumors of parathyroid glands found in association with osteitis fibrosa are of primary significance. It is recognized, however, that overfunction of parathyroid glands may occur in the absence of tumors or other morphologic abnormality.

AUTHOR'S SUMMARY.

EXPERIMENTAL CHRONIC GASTRIC ULCERS IN RABBITS. A. N. FERGUSON, Arch. Int. Med. **49**:846, 1932.

A method for the consistent production of experimental chronic gastric ulcers in rabbits is described. An incision was made in the anterior wall of the stomach at about the junction of the body of the stomach with the pyloric portion. This original incision extended through the serosal and muscular coats down to the submucosa and underlying mucosa, but not through these layers. One edge of the muscular coat was then lifted up, and undercutting was performed through the submucosa for about 2 cm. A circular piece of the exposed mucosa, at least 1.5 cm. in diameter, was then excised by means of scissors, after which the edges of the original incision in the muscular coat were sewed together. The primary mortality from these operations was rather high, death being due to perforation of the stomach at the site of the ulcer, perigastric abscess or incidental infection. A series of lesions (eighteen) was obtained ranging in age from 95 days to 2 years, 1 month and 17 days. A variation in the reparative powers of rabbits with chronic ulcers was noted. In some the ulcers tended to remain chronic, while in others various degrees of healing, even resulting in complete repair, occurred. Experimental chronic ulcers in rabbits tend to decrease in size, when the destructive processes are not too great, even though there is no regeneration of epithelium over the surface of the ulcer. Epithelium forming the margin of a chronic ulcer is composed entirely of foveolar cells. These cells constantly attempt to regenerate and repair the ulcer defect, and are successful when a floor suitable for their growth is formed. Foveolar cells are responsible for regeneration of the epithelium in both acute and chronic experimental ulcers. The essential factor that delays healing and produces chronicity in ulcers is that of destructive forces acting on the floor of the base. There is a constant struggle between these destructive forces and reparative processes. The outcome depends on which one is in excess and gains control.

AUTHOR'S SUMMARY.

THE TESTICULAR HORMONE CONTENT OF TISSUES AND HUMAN URINE. E. B. WOMACK and F. C. KOCH, Endocrinology **16**:267 and 273, 1932.

The method of McGee, Gallagher and Koch for extracting the testicular hormone appears to be the best available at this time. Attempts to obtain active extracts from wheat, yeast, spinach and carrots were unsuccessful. The content

of hormone in the testes of rams varied more than that in the testes of bulls. The hormone has been demonstrated in the testes of fetal bulls. The hormone is present in the urine of men, adolescent boys and normal and pregnant women.

THE HEMOLYTIC ACTIVITY OF THE SPLEEN IN HEMOLYTIC ANEMIA. W. CEELEN, Beitr. z. path. Anat. u. z. allg. Path. **86**:175, 1931.

The author believes the site of hemolysis in the spleen to be the intersinusoidal pulp tissue, which in hemolytic anemia is so stuffed with red blood corpuscles as to appear infarcted. The sinuses are compressed and contain few erythrocytes. Many contain numerous irregularly sized, colorless spherical granules, which give the iron reaction and appear to be intermediate hemolytic products. The constitutional inferiority of the erythrocytes in this disease combined with the prolonged stay in the choked intersinusoidal pulp, due to compression of the sinusoids, favors hemolysis.

W. S. BOIKAN.

EUNUCHOIDISM IN MAN. K. LÖWENTHAL, Beitr. z. path. Anat. u. z. allg. Path. **86**:426, 1931.

Eunuchoidism is a definite constitutional anomaly the anatomic basis of which is an atrophy of the testicles that commences at puberty and proceeds to the extremest grade. The secondary changes in the body commence simultaneously and are dependent on the testicular change. It is apparently a chromosomial anomaly which is inheritable.

W. S. BOIKAN.

FATAL SENSITIVITY TO SUNLIGHT CALLED FORTH BY ENTERAL PORPHYRIN. L. HARANGHY, Centralbl. f. allg. Path. u. path. Anat. **54**:161, 1932.

A 6 year old girl who had a very slow convalescence from measles was suspected of having tuberculosis and was given sun baths for one whole summer. The following spring these baths were resumed, but the child felt so ill after a short exposure that she was taken indoors and promptly felt somewhat better. An unusually severe redness of the exposed parts occurred shortly, and a cough developed. This was in turn followed by icterus and evidences of renal injury. Ten days after exposure to sunlight the child died, and a strain of Flexner's bacillus was cultured from the bowel. This organism was found to form porphyrin in hemoglobin-bouillon mediums. The intestinal bacteria were thus suspected of having formed this substance in the body, and the porphyrin led to a strong photodynamic sensitivity. Exposure to sunlight under these circumstances resulted in marked toxemia. The author cautions against the use of quartz lamps or sunlight in treatment of persons with distress of the bowel and advocates testing the stool for porphyrin.

GEORGE RUKSTINAT.

RELATION OF GENERAL FIBROUS OSTEITIS TO THE PARATHYROID GLANDS. F. W. WICHMANN, Deutsche Ztschr. f. Chir. **235**:619, 1932.

In a woman, 45 years old, with general fibrous osteitis, removal of an adenoma of the parathyroid gland located in the left lobe of the thyroid gland, which was slightly enlarged, was followed by improvement in the condition of the skeleton and a return of the calcium metabolism to normal.

Pathologic Anatomy

THE PATHOLOGIC BASIS OF SYMPTOMS IN NEPHRITIS. J. P. SIMONDS, J. A. M. A. **98**:803, 1932.

Two types of nephritis can be differentiated: (*a*) that in which the essential damage is to the secretory portion of the kidneys, and (*b*) that in which the smaller arteries and arterioles are characteristically involved. This second type

is not so much a primary disease of the kidneys as a generalized disease of the arterioles of the body.

The basic changes in the first type are degenerative and exudative (inflammatory) resulting in increased permeability of the renal filter without retention of nitrogenous products but with loss of albumin in the urine, depletion of blood serum albumin, retention of crystalloids in the tissues and edema. In the second type, the fundamental pathologic change is a hyperplastic sclerosis of the smaller renal arteries and arterioles with narrowing of their lumens, (*a*) reducing blood pressure and blood flow in the glomeruli below that required for adequate filtration and (*b*) interfering with the nutrition and therefore with the function, of the tubules, thus causing retention of nitrogenous waste products.

More elaborate classifications are confusing because they attempt to make separate entities and types out of (*a*) different stages of the same morbid process or (*b*) different combinations of the same fundamental unit pathologic lesions.

If due recognition is given to the fact that nephritis is a progressive disease, it is possible, by means of this simple classification, to make a reasonably satisfactory correlation between its clinical manifestations and their pathologic basis, and to elaborate the principles of rational treatment.

AUTHOR'S SUMMARY.

ELLIPTIC HUMAN ERYTHROCYTES. GARNETT CHENEY, J. A. M. A. **98**:878, 1932.

Elliptic human erythrocytes represent a departure from the round forms usually found. Cases of their occurrence have been rarely reported. It seems probable that they are more common than the meager literature indicates. The hereditary transmission of such unusual red cell forms is emphasized by a report of a family including forty-one members in three generations, fourteen of whom show this bizarre structure in the blood. The transmission is probably by a simple mendelian dominant. Although this condition has been associated with secondary anemia and with sickle-cell anemia, there is insufficient evidence to justify assumption of a relationship. Aside from the unusual erythrocyte forms, nothing remarkable is to be noted in the blood or the bone marrow.

LESIONS OF THE CARDIAC ORIFICE OF THE STOMACH PRODUCED BY VOMITING. SOMA WEISS and G. KENNETH MALLORY, J. A. M. A. **98**:1353, 1932.

Two cases of laceration and ulceration at the junction of the esophagus and the stomach resulted fatally. In the first case, the characteristic longitudinal laceration of the mucosa was acute and unusually deep, rupturing a visible artery and causing death from exsanguination. In the second case, the clinical evidence suggested that an acute laceration which had developed in the past had caused the formation of a chronic ulcer at the junction of the esophagus and the stomach. This ulcer, following an alcoholic debauch and vomiting, ruptured and perforated into the mediastinum, causing bilateral purulent empyema and subcutaneous emphysema. The concept of the mechanism involved in the development of lesions at the cardiac orifice of the stomach described in a previous communication is supported by the clinical course and postmortem observations now reported. Pressure changes in the stomach during disturbed mechanisms of vomiting, together with regurgitation of the gastric juice and the corrosive effect of alcohol, are considered to be responsible for the origin of the lesions described.

AUTHORS' SUMMARY.

HEMORRHAGE INTO THE OVARIAN STROMA IN MITRAL STENOSIS. GEORGE RUKSTINAT, J. A. M. A. **98**:1716, 1932.

Rukstinat describes hemorrhagic infiltration into the stroma of both ovaries in a woman, 38 years old, who died from cardiac decompensation following mitral stenosis.

CYTOLOGIC STUDIES ON RHEUMATIC GRANULOMA. C. MCEWEN, J. Exper. Med. **55**:745, 1932.

Scrapings of subcutaneous nodules from ten patients with rheumatic fever were examined microscopically after being stained with supravital dyes. From the uniform results obtained, the following conclusions have been drawn: Supravital staining of cells from these lesions gives information unobtainable with ordinary histologic methods. The scrapings show a great predominance of certain cells almost entirely devoid of phagocytic power and not characterized by the reactions with neutral red that distinguish monocytes, epithelioid cells and clasmatocytes. Hence they differ from the essential cells of the lesions of tuberculosis and experimental syphilis. These differences are probably functional and developmental rather than genetic. The cells probably arise from the undifferentiated mesenchymal elements of loose connective tissue, although it is possible that endothelial cells take part in their formation in some instances. Since there is little doubt that the subcutaneous rheumatic nodules are pathologically identical with rheumatic granulomas elsewhere in the body, these conclusions are considered applicable also to the Aschoff body cells of the myocardial submiliary nodules.

AUTHOR'S SUMMARY.

COMPLETELY HEALED DISSECTING ANEURYSM OF THE AORTA. T. SHENNAN, J. Path. & Bact. **35**:161, 1932.

In a man 64 years of age there were recurrent hemorrhages into and along the walls of the aorta. The original hemorrhage into the mediastinum and along the adventitia of the extrapericardial thoracic aorta, occurring about six months before admission, had organized to form a dense layer of connective tissue abutting on and buttressing the media. The point at which the escape of blood took place could not be identified. A second hemorrhage dissecting along the outer layers of the media internal to the thickened adventitia had occurred eight weeks before death, and in the interval had organized completely with obliteration of the sac. This hemorrhage originated in a rupture, now healed, of the inner coats on the wall opposite to the ligamentum arteriosum. Shortly before death a third rupture occurred on the right posterior wall in the neighborhood of the ligamentum arteriosum, and the resulting hemorrhage into the media internal to the previous organized layer formed an elongated hematoma in the wall of the descending aorta. This caused a bulging inward of the walls at the upper end of the descending aorta, producing a condition similar to isthmus stenosis, which so increased the pressure in the ascending aorta that a fourth rupture occurred proximal to the reflexion of the pericardium in the anterior wall of the bulbus. The resultant dissecting aneurysm in the wall of the ascending aorta ruptured into the pericardium and caused sudden death. There was no atheromatous change in the area of the wall involved in the proximal rupture, and none of the other ruptures was specially related to atheromatous patches or ulcers. Dissecting aneurysms originating in such ulcers are extremely rare, though this is commonly believed to be a frequent mode of origin.

AUTHOR'S SUMMARY.

THE PATHOLOGY OF ANEURYSM: A REVIEW OF 167 AUTOPSIES. H. G. GARLAND, J. Path. & Bact. **35**:333, 1932.

The material analyzed in this article comes from 12,000 consecutive autopsies at all ages from 1910 to 1930. The 167 cases of aneurysm are analyzed according to location and nature of the underlying lesion. Eighty-six of the cases were syphilitic; of 78 cases of aneurysm of the thoracic aorta, 91.3 per cent were syphilitic.

BONE WITHIN A RENAL CALCULUS. G. STUART and K. S. KRIKORIAN, J. Path. & Bact. **35**:373, 1932.

A description is given of a case of renal calculus containing living bone.

AUTHORS' SUMMARY.

ABNORMALITIES OF THE MOUSE SUPRARENAL. R. WHITEHEAD, J. Path. & Bact. **35**:415, 1932.

The abnormalities noted in the suprarenal glands of 477 untreated mice are described. They include medullary cells in the cortex, inflammatory spindle cells, cortical hypoplasia or atrophy and a hitherto undescribed type of tumor in the medulla.

AUTHOR'S SUMMARY.

THE FORMATION OF THE ASBESTOSIS BODY IN THE LUNG. S. R. GLOYNE, Tubercle **12**:399, 1931.

The absence of asbestosis bodies in crude asbestos makes it practically certain that they are produced in living tissues from inhaled asbestos fibers. Gloyne believes that they are formed in the lung by deposition of certain materials that tend to thicken the fiber, thus causing the fissure or cracking of the deposited material and giving rise to the segments. There is evidence that iron is a component of this material.

H. J. CORPER.

THE LYMPHATIC VESSELS OF THE FALLOPIAN TUBE. M. A. PELLÉ and O. PELLÉ, Ann. d'anat. path. **8**:605, 1931.

The drainage of the lymph of the fallopian tube is performed by a principal external route leading to the right and left lateral aortic ganglions, by a middle route ending in the middle chain of the external iliac ganglions and by an internal route leading to a hypogastric ganglion.

There are often anastomoses between the lymphatic vessels of the tube and the perirenal capsule, which explains the ease with which a tubal infection reaches the perirenal fat. It likewise explains the frequency of renal pain in the course of even light cases of salpingitis, and also possibly the origin of some perinephric phlegmons regarded as "primary."

The tubal lymphatic vessels have no connection with the appendix; they communicate with those of the uterus and of the ovary.

B. M. FRIED.

GENERAL CHARACTERISTICS OF MALIGNANT GRANULOMA. M. FAVRE and P. CROIZAT, Ann. d'anat. path. **8**:838, 1931.

Malignant granuloma (Favre and Croizat use this term for malignant lymphogranulomatosis) does not involve the lymphoid tissues only but more generally the mesenchyma, the supporting substances and the reticulo-endothelial system in the broad sense of this word. It spreads in a mesenchymatous medium, and the first invasive lesion may be extragranular, intradermic.

The granuloma has a peculiarly active influence on the connective tissue, "reverting" the connective tissue cells into undifferentiated elements, histiocytes and hemohistioblasts, which evolve and differentiate into granulocytes, erythroblasts and even megakariocytes. In the formation of the lesions, cells differentiated in situ play a more important rôle by far than those brought by the blood stream.

The histologic reactions appear to be inflammatory, resulting from local action of the granulomatous virus (?). The peculiar polymorphism of the lesion, its changeable and "fluctuating" aspect, is of interest when compared with neoplastic pictures which are constant. Two parallel reactions are noticed, one inflammatory and another designated as neoplastic. In fact, the only cell that appears to be neoplastic is that of Sternberg. However, even this cell is not a point of departure but an expression in the evolution of the disease. The cell should be regarded as an evolving form of the hemohistioblast. Malignant granuloma is on the borderline between inflammation and neoplastic formation. Favre and Croizat discuss in detail different pathologic and clinical aspects of the disease.

B. M. FRIED.

THE PATHOLOGIC ANATOMY OF THE HUMAN THYMUS. P. BASTENIÉ, Arch. Internat. de méd. expér. **7**:273, 1932.

The disappearance of the thymocytes in the course of pathologic involution of the thymus is not the result of their emigration but of their destruction in situ. The genesis of the corpuscles of Hassall is connected with the destruction of the thymocytes. Of mesodermic origin, appearing soon after the pyknosis of the small thymic cells, the corpuscles of Hassall do not appear to have any secretory significance. Thymic involution follows any general disturbance of the body and is not peculiar to any particular disease or intoxication. So-called types of involution are disease stages of the same process. In the course of pathologic involution, the thymus presents the same elastic reactions as in physiologic involution, the indications being that in both conditions it acts as a regulator in the dispensation of nuclein.

SPECIFIC BONE MARROW CHANGES IN AGRANULOCYTOSIS. E. OPPIKOFER, Beitr. z. path. Anat. u. z. allg. Path. **85**:165, 1930.

Three cases of acute agranulocytosis were studied microscopically with the following results: The disappearance of the granulocytes was uniform in all organs and blood vessels. The characteristic picture of the bone marrow showed involvement of the myeloblasts in severe degenerative changes ranging to complete necrosis, absence of granulocytes and undisturbed erythropoiesis. The spleen showed a plasma cell reaction with absence of leukocytes. These results speak for an essential agranulocytosis on a toxic basis.

W. S. BOIKAN.

THE EFFECT OF POTASSIUM IODIDE ON THE THYROID GLAND OF THE RAT. F. H. IRSIGLER, Beitr. z. path. Anat. u. z. allg. Path. **85**:220, 1930.

Irsigler studied the histologic changes in the thyroid gland of the rat by means of potassium iodide. Intraperitoneal administration was more active in smaller dosage than peroral. With the small dosage used by American investigators, a marked stimulation of the thyroid gland, as evidenced by numerous nuclear divisions, was obtained. With a still smaller dosage, however, Irsigler avoided obvious cellular stimulation, but obtained increased accumulation of colloid in the vesicles. True exophthalmic goiter was not produced.

W. S. BOIKAN.

CARDIAC LESIONS IN SCARLET FEVER, STREPTOCOCCUS INFECTIONS AND RHEUMATIC GRANULOMATOSIS. T. FAHR, Beitr. z. path. Anat. u. z. allg. Path. **85**:445, 1931.

The focal and diffuse histiocytic proliferations in the heart first described by Fahr in scarlet fever are regarded by him as allergic reactions to the streptococci usually associated with scarlet fever. These changes are, however, in marked contrast to the Aschoff nodule in rheumatic fever. This nodule is as specific a granuloma as the lesions of tuberculosis or of Hodgkin's disease.

W. S. BOIKAN.

BONE MARROW IN THE SUPRARENAL GLANDS. J. SOÓS, Beitr. z. path. Anat. u. z. allg. Path. **85**:611, 1930.

Soós reports the occurrence in otherwise normal suprarenal glands of pea-sized to walnut-sized circumscribed nodules of yellow, red and mixed bone marrow showing myelopoiesis and erythropoiesis. The yellow nodes have previously been called lipomas. The opinion is expressed that the nodes originate from microscopic foci of bone marrow.

W. S. BOIKAN.

TELANGIOSTENOSIS—THE UNDERLYING PROCESS IN ENDARTERITIS OBLITERANS AND OTHER VASCULAR DISEASES. S. KROMPECHER, Beitr. z. path. Anat. u. z. allg. path. **85**:646, 1930.

Telangiostenosis is a primary disease of the small blood vessels, arterial and venous, which leads to gangrene of the extremities and organic insufficiency. The stenosis is produced by intimal elastoblast proliferation and formation of elastic membranes. The elastoblast is the earliest cell to differentiate from the vascular mesenchyme. Thrombosis is always secondary. Intervascular increase of elastic elements occurs concurrently and is termed elastofibrosis. Telangiostenosis by itself or in association with atherosclerosis is considered the underlying process of endarteritis obliterans, arteritis obliterans, thrombo-angiitis obliterans, malignant nephrosclerosis and scleroderma.

W. S. BOIKAN.

AORTIC LIPOID DEPOSITS IN CHILDREN. A. SSOLOWJEW, Centralbl. f. allg. Path. u. path. Anat. **53**:145, 1931.

Ssolowjew believes the fatty specks found in the aortas of young children are the result of a milk diet high in cholesterol. The proof was furnished by the aortas of suckling guinea-pigs, which contained microscopic fat droplets in the interstitial tissue of the intima and inner portions of the media. Such deposits were increased by feeding pregnant guinea-pigs egg yolk and milk. Additional support is given to this theory by the finding of varying amounts of fat in the hepatic cells and hepatic duct cells of such sucklings, whereas fat is found only in the Kupffer cells of guinea-pigs on a diet of grains and vegetables. Egg yolk and milk apparently occasion the appearance of fat globules even within the intimal cells of the aorta and give rise to macroscopically demonstrable deposits.

GEORGE RUKSTINAT.

ABNORMAL TISSUE FRIABILITY, HYPOFIBROSIS UNIVERSALIS. C. BENEKE, Centralbl. f. allg. Path. u. path. Anat. **53**:177, 1931.

The patient was 49 years old at death and had a rather unusual history. At 18 years, she had had typhoid fever and thereafter remained well until she was 36. Then severe gastro-intestinal symptoms occurred, accompanied by vomiting and bowel movements as many as twenty-two per day. Such attacks occurred again ten, eleven and twelve years later. Thirteen years later colic, icterus and loss of weight led to operative treatment, and a gastro-enterostomy was performed with difficulty. During this operation, the serosa of the bowel and stomach became detached at the least touch, and a retractor applied to the liver caused a tear in it. Two days later death occurred from peritonitis and anemia. At autopsy the skin of the neck was almost entirely devoid of cutis; the fat of the body was normally abundant, except on the hands. The abdominal cavity contained about 500 cc. of free blood. The mesentery tore like spider-web; the abdominal muscles could be pulled away from the abdominal wall with very little force; the myocardium, aorta, liver and kidney were very friable. The spleen could be torn from the body easily; the duodenum burst when its removal was attempted. The friability of the tissues was due to the small amount of collagenic fibers.

GEORGE RUKSTINAT.

PURULENT AORTITIS. F. HAUBRANDT, Centralbl. f. allg. Path. u. path. Anat. **53**:327, 1932.

The classification of the 100 reported cases of purulent aortitis includes extension to the aorta from a neighboring infection, most commonly from an aortic endocarditis extending to the aortic intima or from a purulent process outside of the aorta extending to the adventitia. Less frequently the infection is carried in the blood of the aorta, and rarely by the vasa vasorum. Haubrandt reports a case of the commonest and then one of the rarest forms. The latter resulted from pneumococcic pneumonia of the right upper lobe. The cocci settled in the scars

of an old syphilitic aortitis and caused purulent aortitis. The etiologic factors were obvious; first pneumonia and then purulent aortitis, which was so extensive and protracted as to occasion purulent pericarditis.

GEORGE RUKSTINAT.

AGRANULOCYTIC BLOOD PICTURE FOLLOWING TREATMENT WITH ARSPHENAMINE. CARL OESTEREICH, Folia haemat. **44**:137, 1931.

In a patient with tabes dorsalis there developed typical agranulocytosis following antisyphilitic treatment with a German arsphenamine. The case differed from those described by Schultz, in that there were no lesions of the mucous membranes and no icterus. The platelets, too, were diminished in number without, however, causing hemorrhages. It is certain that preparations of benzene and arsenic used in the treatment of syphilis are liable to induce a disease of the granulocytic apparatus.

B. M. FRIED.

SYPHILIS OF THE LUNG. F. LANDSBERG, Virchows Arch. f. path. Anat. **277**:583, 1930.

In the case presented, the clinical diagnosis of syphilis of the lung was based on the physical and roentgenologic findings and on the strongly positive serologic reactions. The man was 55 years of age and had contracted the syphilitic infection at the age of 20 years. Necropsy revealed, in addition to syphilitic mesaortitis, marked scarring and contraction of the lung, with gummatous caseation and productive endarteritis. Spirochetes and tubercle bacilli could not be demonstrated by the appropriate staining methods.

W. SAPHIR.

LIPOID CELLULAR HYPERPLASIA IN LYMPHOGRANULOMATOSIS. H. FREIFELD, Virchows Arch. f. path. Anat. **277**:595, 1930.

In two cases of lymphogranulomatosis with characteristic histology, the reticuloendothelial cells of the spleen and lymph nodes had proliferated and contained large quantities of lipoid material. The enlarged cells resembled somewhat those of Gaucher's disease.

W. SAPHIR.

THE PYELONEPHRITIC CONTRACTED KIDNEY. M. STAEMMLER and W. DOPHEIDE, Virchows Arch. f. path. Anat. **277**:713, 1930.

Staemmler and Dopheide review the literature and present cases of their own. The gross characteristics of the kidney contracted as the result of pyelonephritis are: variability of the alterations present in the two kidneys; diffuse distention of the renal pelvis and calices without apparent obstruction; irregularity and granulation of the surface of the kidney; irregular contraction of the parenchyma, and thickening of the mucosa of the pelves, ureters and bladder. The histologic changes noted were: chronic inflammation of the pelvis and calices, with epithelial hyperplasia and metaplasia; chronic productive inflammation of the medulla, with scarring of the pyramids and connective tissue proliferation at the corticomedullary junction, and chronic inflammation of the cortex, leading to destruction of parenchyma and glomeruli and their replacement by scar tissue.

W. SAPHIR.

GIANT CELL PNEUMONIA IN AN ADULT. M. DUGGE, Virchows Arch. f. path. Anat. **277**:757, 1930.

This is the first recorded instance of giant cell pneumonia in an adult. The disease has been previously observed only in children. A farmer, 30 years of age, who had suffered for many years with asthma, died with symptoms of pneumonia. Necropsy revealed advanced chronic bronchopneumonia with bronchiolitis, chiefly of the upper lobes. There was extensive development of granulation and con-

nective tissue. Giant cells containing cholesterol crystals and concentric iron and calcium incrustation bodies were the most striking feature of the histologic picture. The giant cells were embedded in the granulation tissue and, according to Dugge were derived from the endothelium of the granulation tissue. The giant cells of the organizing pneumonia of children, he believes to be derived from the alveolar epithelium. Such alveolar epithelial giant cells were seen also in the case reported (See Du Bois, Franklin S.: Chronic Bronchitis with Foreign Body [Elastic Fibers] Reactions in the Lungs, ARCH. PATH. **12**:222, 1931).

W. SAPHIR.

Pathologic Chemistry and Physics

IRON IN THE LIVER AND IN THE SPLEEN AFTER DESTRUCTION OF BLOOD AND AFTER TRANSFUSIONS. S. A. GLADSTONE, Am. J. Dis. Child. **44**:81, 1932.

Livers obtained at autopsies on fetuses and infants were studied microscopically and chemically to determine the variations in the amount of iron present and the factors on which the variations depend. There is no evidence microscopically or chemically of large or progressive depositions of iron in the liver during the last four months of intra-uterine life. Exclusive of iron as hemoglobin, the entire liver of the mature new-born infant contains on the average about 32 mg. of iron. The largest amounts of iron are found in the liver from one to ten weeks after birth, and these are believed to depend on postnatal intravascular destruction of blood. Hemosiderosis of the liver may also result from hemorrhages into the tissues or cavities of the body of the fetus or infant, and during fetal life it may result from similar hemorrhages in the mother, the liberated iron reaching the fetal liver via the placenta. Hemosiderosis of the spleen and the liver follows transfusions of blood, and the amount of iron found in the liver is influenced by the size and frequency of the transfusions. The appropriation and utilization of transfused blood are discussed. It appears that the changes occurring during the first three months of human life are comparable to the changes that occur during the first six days of postnatal life in the rabbit, namely, a doubling of the body weight, a moderate increase in the total hemoglobin, a marked decrease in the percentage of hemoglobin and an early loss of iron followed by a progressive increase of hemoglobin iron but more particularly of nonhemoglobin iron.

AUTHOR'S SUMMARY.

HISTOCHEMICAL STUDIES BY MICROINCINERATION OF NORMAL AND NEOPLASTIC TISSUES. G. H. SCOTT and E. S. HORNING, Am. J. Path. **8**:329, 1932.

The results obtained from this investigation are of interest, as they have demonstrated that functional differences between cancer and normal tissues are exhibited inorganically by marked variations in their inorganic content. An additional feature is the close similarity between developing embryonic cells and cancer cells—a similarity which is mainly due to the distribution and arrangement of mineral salts. Both of these cells are characterized by an extraordinary variation in the intensity, concentration and orientation of their inorganic constituents, and contrast greatly, on the other hand, with healthy adult tissue in the appearance of the mineral elements, which in the latter remain proportionally fixed. This "inorganic reversion" of the cancer cell, as revealed by micro-incineration, is interesting in view of Cohnheim's theory to the effect that malignancy depends on the retention of small groups of cells of embryonal character.

AUTHORS' SUMMARY.

CHOLESTEROL CONTENT OF BLOOD IN EPILEPSY AND IN FEEBLEMINDEDNESS. H. GRAY and L. C. MCGEE, Arch. Neurol. & Psychiat. **28**:357, 1932.

One hundred and eight samples of blood from feebleminded patients over 20 years of age and 623 samples from that of epileptic patients over 20 years of age,

taken at various intervals after meals, have been studied by Bloor's method (without saponification) for cholesterol content, in contrast with blood from normal persons. It was found that cholesterol is sufficiently stable to permit the use of samples of oxalate plasma that has stood four days or of whole blood that has stood a week or longer (three weeks). The adolescent persons with epilepsy had a slightly lower level of cholesterol than the adults. Within one hour after an epileptic seizure the cholesterol average reached a low point. It was somewhat higher at intervals of from two hours to one week than during the first hour, and again it was at a lower level at intervals of from one to four weeks. At intervals of more than one month after seizures, the cholesterol average rose to 172 mg. (in normal contrasts it was 190 mg.). The influence of meals was found to be negligible. The average cholesterol value of the whole blood was found to be 194 mg. per hundred cubic centimeters for normal men, 165 mg. for persons with epilepsy and 154 mg. for feebleminded persons. After convulsions, there is a drop in cholesterol, followed by a gradual rise which continues for a month though it does not reach the average value for normal persons, the difference being about 10 mg. Near the attack the ratio is higher. In other words, the cholesterol in the blood of persons with epilepsy is low, and in feebleminded persons it is even lower. The high fat diet recommended in the treatment of epilepsy is thus justified also on theoretical ground.

GEORGE B. HASSIN.

ESTIMATION OF PROTEINS BY THE PRECIPITIN REACTION. G. L. TAYLOR, G. S. ADAIR and M. E. ADAIR, J. Hyg. **32**:340, 1932.

The amount of crystallizable albumin in egg-white and the amount of total globulin in horse serum have been estimated by means of the precipitation reaction. The results are in good agreement with those obtained by other methods. For such estimations it appears advisable to use only antiserums prepared against individual proteins.

AUTHORS' SUMMARY.

CAUSES OF CELL DEATH IN IRRADIATED HUMAN TISSUE. B. D. PULLINGER, J. Path. & Bact. **35**:527, 1932.

In living vascular tissues, as opposed to in vitro preparations and young embryonic cells, hyperemia is an essential reaction to therapeutic irradiation with radium and x-rays. Thin-walled, loosely supported capillaries and veins are most readily affected and react in deep structure as well as at surfaces. If endothelial injury follows excessive distention, hyperemia is succeeded by exudation of serum, extravasation of blood and intravascular thrombosis. All effects following irradiation are related to these two phases, namely, vascular stimulation and vascular degeneration. Problems which remain to be solved are concerned with the particular kind of radiation which starts the reaction and with the immediate hyperemic stimulus. Is the former beta or gamma? Is the latter physical or due to liberation of a chemical product such as histamine?

AUTHOR'S SUMMARY.

BILE PRECIPITATION AND BILIARY CALCULI. C. E. NEWMAN, Beitr. z. path. Anat. u. z. allg. Path. **86**:187, 1931.

In human bile, the ratio of bile acids to cholesterol is within certain limits a constant one. Hepatic injury may disturb this ratio in favor of relatively increased cholesterol and thus favor the formation of calculus. The bile from gallbladders containing calcium pigment cholesterol stones shows a relatively decreased bile acid content with consequent decreased ability to keep the cholesterol in solution. Bile in pigment calculosis shows a normal ratio of constituents. Sediments are found in practically all bile and more often in normal than in abnormal gallbladders. Neither these nor the so-called microlithia (spheroid bodies from 10 to 30 microns in diameter) have any relation to the formation of biliary stone.

W. S. BOIKAN.

URIC ACID CONTENT OF BLOOD FROM THE UMBILICAL CORD. IWAN MANOLOFF, Frankfurt. Ztschr. f. Path. **42**:188, 1931.

Determinations were made in 120 cases. In 66, the uric acid content was less, and in 54 it was more than 4 mg. per hundred cubic centimeters. In eleven children, the uric acid content amounted to from 5.5 to 8.52 mg. per hundred cubic centimeters. The author believes that the average uric acid content in the newborn is higher the longer the labor lasts. In children of primiparae the uric acid content, as a rule, is higher than 4 mg. per hundred cubic centimeters.

O. SAPHIR.

LIPOLYTIC ACTIVITY OF BLOOD SERUM AND CEREBROSPINAL FLUID AFTER DEATH. E. BACH and L. LUSZTIG, Virchows Arch. f. path. Anat. **280**:325, 1931.

In preliminary experiments the lipolytic activity of the blood serum was determined one or two days before death and again after death; the changes noted fell within the limits of error of the method used, which was that of the splitting of tributyrin. Repeated examinations up to twenty-four hours after death also showed no change in lipase content. In general, the lipolytic activity of the serum bore a direct relation to the nutritional condition, being high in bodies with much fat and low in those with little adipose tissue. In cachexia and uremia, the lipase content of the serum was decreased; in acute febrile infectious diseases it was increased. In early tuberculosis it was normal or only slightly decreased, whereas in late tuberculosis with caseation it was greatly decreased or absent. The lipolytic activity of the cerebrospinal fluid was less than that of the blood serum, but in general rose or fell with the latter. The authors suggest that postmortem studies of lipase may be of value in the study of pathologic fatty change, intoxications, and a variety of diseases.

O. T. SCHULTZ.

LEAD CONTENT OF HUMAN BONE. E. BARTH, Virchows Arch. f. path. Anat. **281**:146, 1931.

The P. Schmidt micromethod was used for the determination of the lead content of bones of persons of various ages who had never had lead poisoning or close contact with lead in industry. The bones of infants contained 0.01 to 0.03 mg., those of young adults from 0.03 to 0.05 mg., and those of older adults from 0.08 to 0.14 mg. The same slight progressive increase was noted in the inhabitants of villages without a central water supply as in cities. The author believes that the lead is derived from foods that normally contain small quantities of lead.

O. T. SCHULTZ.

CALCIUM CONTENT OF THE ARTERIES OF THE UTERUS. W. ZINKANT, Virchows Arch. f. path. Anat. **281**:911, 1931.

Quantitative chemical methods yield accurate information respecting the content of the estimated substance in a tissue, but give little information respecting the distribution of the substance in relation to the tissue elements. Histochemical and histologic methods may permit the detection of certain substances and may make it possible to study the distribution of the substances, but such methods may fail to detect smaller quantities of substance that the chemical method reveals. The Schultz-Brauns method of ashing frozen sections of fresh, unfixed tissues is said to give more accurate information on the presence and localization of certain substances, especially calcium and iron, than other methods. Zinkant applied this method to a study of the calcium content of the arteries of the uterus. By this method calcium was found to be present in the second and third decades of life, at a time when the usual histochemical methods fail to reveal its presence. The

element is present in both media and intima, and increases progressively with age. During the fifth decade, when the usual methods may reveal the presence of large masses of calcium in the media, the Schultz-Brauns method demonstrates the presence of calcium in the smaller arteries and even in the arterioles. No relation between the calcium content of the uterine arteries and the number of previous pregnancies could be detected.

O. T. SCHULTZ.

GALACTOSIDES AND LIPOID METABOLISM. P. KIMMELSTIEL, Virchows Arch. f. path. Anat. **282**:402, 1931.

In studies of lipoid metabolism and of the lipoid content of pathologic tissues, most attention has been paid to cholesterol and its esters. In some of the pathologic states characterized by lipoid infiltration, the phosphatides and cerebrosides have received attention, but not as much as their importance in general lipoid metabolism and in the pathology of the lipoids warrants. The object of the studies reported by Kimmelstiel has been the lipoids characterized by the presence of a galactose molecule, the galactosides, which have been more often referred to in pathologic literature as cerebrosides. The cholesterol, phosphatide and galactoside fractions of the lipoid complex were determined quantitatively in the human aorta at different ages. The cholesterol fraction was largest, the phosphatide next, and the galactoside third. The three fractions increased *pari passu* with the degree of lipoid infiltration evident to the naked eye. Cholesterol increased disproportionately and markedly when atheromatous degeneration was evident. The high cholesterol content does not appear until degeneration and death of tissue have occurred, with disturbance in the interrelations of the elements of the lipoid complex. In acute feeding experiments, in which pure cholesterol in sesame oil was fed to young rabbits, the phosphatide and galactoside content of the liver increased 89 and 83 per cent, respectively; cholesterol, only 50 per cent. In the kidney there was no appreciable increase of cholesterol, but phosphatide and galactoside increased 43 and 53 per cent, respectively. Comparative physicochemical studies of different lipoids revealed that the galactosides have an intermediate position in the series of hydrophobe and hydrophil colloids. The physicochemical properties of the galactosides are an indication of their importance in lipoid metabolism. In atherosclerosis, cholesterol does not have the significance that has been attached to it, since the increase that has been considered significant does not occur until tissue has died. Previous to the stage of local tissue death, the phosphatides and galactosides increase proportionately as much as does cholesterol.

O. T. SCHULTZ.

THE LIPOID CHEMISTRY OF XANTHOGRANULOMATOSIS. H. KLEINMANN, Virchows Arch. f. path. Anat. **282**:613, 1931.

Kleinmann made quantitative determinations of the lipoids of tissues from the case of xanthogranulomatosis reported by Ighenti (*Virchows Arch. f. path. Anat.* **282**:585, 1931). His results are in general agreement with those of Chiari. The essential findings were: an increase in total lipoids due to a relative and absolute increase in cholesterol and its esters, a reversal of the ratio of cholesterol ester to cholesterol as compared with normal tissues, and a reversal of the ratio of cholesterol to lecithin as compared with Niemann-Pick's disease. The ratio of cholesterol to lecithin was 5.85:1, as compared with 1:9.3 for the spleen of Niemann-Pick's disease. The ratio of cholesterol ester to cholesterol was 5.08:1, as compared with from 1:2 to 1:4 for normal tissues. The total lipoids of the spleen were not increased, but the ratio of cholesterol to lecithin was altered, being 2.7:1. For the normal spleen this ratio is 1:1.8, and for the spleen of Niemann-Pick's disease, 1:9.3. The ratio of cholesterol ester to cholesterol was 3.5:1. The total cholesterol of the liver was increased, being 3.86 per cent as compared with 1.28 per cent for the normal liver. The ratio of cholesterol to lecithin was 3.7:1.

O. T. SCHULTZ.

HISTOCHEMICAL STUDY OF URIC ACID INFARCTS OF THE KIDNEY OF THE NEW-BORN INFANT. SABINE EHRLICH, Virchows Arch. f. path. Anat. **283**:194, 1932.

The material that forms the so-called uric acid infarcts of the kidney of the new-born infant consists of rounded, concentrically laminated and radially striated concretions in the lumens of the straight tubules. Small numbers of similar concretions are found also in the tubules of the cortex. Microchemical methods demonstrated that the material is composed chiefly of uric acid and sodium, to which calcium, phosphoric acid and oxalic acid are added.

O. T. SCHULTZ.

AMOUNT AND ARRANGEMENT OF THE BROWN PIGMENT OF HEART MUSCLE. O. OTTO, Virchows Arch. f. path. Anat. **283**:611, 1932.

Brown pigment is present in normal cardiac muscle at the latest by the twentieth year of age. It is situated at either one or both poles of the nucleus. In the actively functioning hypertrophied myocardium, the formation of pigment proceeds more slowly than in normal muscle. If the mass of pigment is situated at one pole of the nucleus in the normal cell, it becomes bipolar when the muscle hypertrophies. When the action of the hypertrophied muscle becomes weakened or insufficient, pigment deposition is increased, the new-formed pigment being at first localized at one pole of the nucleus.

O. T. SCHULTZ.

IRON CONTENT OF THE ARTERIOSCLEROTIC AORTA. I. H. PAGE and W. MENSCHICK, Virchows Arch. f. path. Anat. **283**:627, 1932.

According to older histochemical investigations, the iron content of bone is temporarily increased during physiologic calcification. Twenty-four aortas of persons from 19 to 82 years old were analyzed quantitatively for their total content of iron. Three of the aortas were normal; the rest exhibited varying degrees of degeneration and calcification. Organic phosphorus was also determined. The iron content was not increased, and there was no parallelism between the degree of calcification and the quantity of total iron or that of loosely bound iron present. Organic phosphorus increased with the degree of calcification.

O. T. SCHULTZ.

RESPIRATORY MECHANICS OF THE LUNG. O. THIES, Virchows Arch. f. path. Anat. **284**:772 and 796, 1932.

The first communication is a critical review of the literature dealing with the measurement of mechanical factors operative in the lungs during respiration. The second is an account of the author's attempts to evaluate some of these factors in the lung after death by means of the Gildermeister elastometer, which measures the elasticity of a tissue in terms of changes in hardness. The work reported represents a considerable amount of labor and an ingenious technic, but it resulted in no very definite conclusions.

O. T. SCHULTZ.

CHEMICAL CHANGES IN PARENCHYMATOUS DEGENERATION. V. UHER, Virchows Arch. f. path. Anat. **284**:880, 1932.

The potassium content of the liver in a state of cloudy swelling is relatively increased; the sodium content, relatively decreased. This disturbance in the relation of potassium and sodium ions leads to increased retention of water by the cell, to increased dispersion of the plasma colloids, and to maximum swelling of the colloids.

O. T. SCHULTZ.

BENCE-JONES PROTEIN. OTTO JERVELL, Norsk mag. f. lægevidensk. **93**:622, 1932.

In a case of multiple myeloma, Bence-Jones protein was found in the blood and urine. Spontaneous crystallization of the protein took place when the urine was allowed to stand for some time. The crystals were easily dissolved in alkaline solution; on adding acetic acid, precipitation occurred again, with the reformation of crystals in a short time. The crystals formed of finer and larger needles as well as spheres and boat shapes. Crystals recrystallized three times and dried in the air were employed for determining the iso-electric point, which was found to lie between p_H 4 and p_H 4.25. The serum coagulated on heating to 56 C. The total quantity of protein in the serum was 9.08 per cent with 5.09 per cent globulin and 3.99 per cent albumin. On mixing 0.5 cc. of serum with 4.5 cc. of salt solution and two drops of 2 per cent acetic acid, a white precipitate formed after two or three hours at 58 C. Control serum treated in this way gave no precipitate. The Bence-Jones protein was obtained by heating the diluted and acidulated serum to the boiling point and filtering over a boiling water bath; from the filtrate the protein was salted out with ammonium sulphate.

Microbiology and Parasitology

BRAIN TO BRAIN TRANSMISSION OF THE SUBMAXILLARY GLAND VIRUS IN YOUNG GUINEA PIGS. N. P. HUDSON and F. S. MARKHAM, J. Exper. Med. **55**: 405, 1932.

The virus of the submaxillary glands of guinea-pigs was transmitted serially from brain to brain in young guinea-pigs. Successful transmission was shown by nervous symptoms, death and typical meningo-encephalitis. Increase in virulence of the virus or adaptation to the brain tissue was not observed. Fifteen days or more after cerebral inoculation, typical cellular inclusions were found in the salivary gland.

THE ASSOCIATION OF PNEUMOCOCCI, HEMOPHILUS INFLUENZAE, AND STREPTOCOCCUS HEMOLYTICUS WITH CORYZA, PHARYNGITIS, AND SINUSITIS IN MAN. L. T. WEBSTER and A. D. CLOW, J. Exper. Med. **55**:445, 1932.

Pneumococci, H. influenzae and S. hemolyticus are known to be frequent inhabitants of the upper respiratory tract, but most workers have not recognized any definite relationships between their presence and coryza, sore throat, influenza and sinusitis. Dochez, Shibley and Mills, however, in experimental studies of common cold, stated that in both spontaneous and experimentally induced "colds" in anthropoid apes, the "most significant change observed has been the increase of activity on the part of the potential pathogens habitually present in the throat flora. Coincident with the appearance of symptoms, pneumococci, S. hemolyticus, and B. pfeifferi have developed in greatly increased numbers and have spread over a wide area of the nasopharyngeal mucous membranes. These organisms became at this time conspicuous even in the nose, where they are seldom or never present under normal conditions. The same phenomena have not been observed in human beings." The essential facts of the present observations are that persons free from pneumococci, H. influenzae and S. hemolyticus are in general free from coryza, sore throat, influenza and sinusitis; that persons who are occasional or periodic carriers of these organisms may not show the presence of the organisms in tests over long periods of health, but generally yield positive cultures during or following attacks and subsequently again give negative results in tests; finally, that persons who are chronic carriers show, during these illnesses, increasing numbers of organisms in the throat and extension of the organisms to the nose. That these organisms may be the actual incitants has been claimed by Park. That they are secondary invaders is the view of Shibley, Mills and Dochez, who stated as a result of their experimental work on this subject that "the most important

significance of viruses of this type (common cold) seems to lie in their capacity to incite activity on the part of the more dangerous pathogenic organisms that infect the upper respiratory tract." The present observations bring out the intimate relationship between these pathogens and symptoms of disease of the upper respiratory tract, but do not disclose the nature of the relationship. Finally, an addition has been made to the knowledge of the mode of spread of these organisms. A focus of growth and dissemination has been determined in the nasal passages and throat of the person who suffers from chronic disease of the upper respiratory tract, and increases in numbers of the organisms at the focus and their spread to contacts have been related to the winter season and to the occurrence of symptoms in the carrier. The observations suggest that the dosage of these organisms in a community is controlled by the resistance of the carrier and of the contacts. This view is an agreement with the facts derived from studies of native animal infections.

AUTHORS' SUMMARY.

THE AGENT OF FOWL LEUCOSIS. J. FURTH and H. K. MILLER, J. Exper. Med. **55**:465, 479 and 495, 1932.

Concentration in Blood Cells and Plasma (J. Furth.).—The concentration of the transmitting agent of leukosis in fowls, as determined by titration, was approximately the same in suspensions of blood cells and in cell-free plasma; the smallest amount of plasma producing leukosis was 0.000001 cc., and of cell suspension, 0.00001 cc. This observation excludes the possibility that transmission of leukosis by plasma is due to the presence of a small number of leukemic cells in the plasma. The success of inoculations with plasma (20 to 28 per cent of fowls) was, within wide limits, independent of the amount injected (10^{-1} to 10^{-6} cc.). The percentage of successful inoculations with varying quantities of plasma was lower than with corresponding amounts of suspensions of cells (from 33 to 71 per cent). When plasma containing the transmitting agent was injected in decreasing amounts, the period of incubation of the leukosis was conspicuously lengthened. With decreasing amounts of a suspension of leukemic cells, the period of incubation was not so frequently or so greatly prolonged.

Filtration of Leukemic Plasma (J. Furth and H. K. Miller).—The agent transmitting leukosis readily passed all types of silicious filters. Filtration was particularly successful when the plasma was freed from particles and substances that would otherwise obstruct the pores of the filter. Filtration through fine filters seemed to be facilitated by preceding filtration through coarse filters. A comparison of the periods of incubation of leukosis produced by unfiltered plasma and plasma passed through silicious filters showed that as a result of filtration, the period of incubation was somewhat prolonged. This suggests a slight or moderate decrease in the concentration of the transmitting agent in the plasma caused by filtration. Filtration through collodion membranes indicated that the agent transmitting leukosis is much smaller than the virus of bovine pleuropneumonia (250 microns), and that it approximates the size of bacteriophage.

Resistance to Desiccation and Other Factors (J. Furth).—The filtrable agent transmitting leukosis resisted drying, retaining its activity for at least fifty-four days. The conditions of successful desiccation have not been precisely ascertained. By the addition of glycerin, the agent could be preserved for at least one hundred and four days. It was not inactivated by freezing in liquid air. At 37.5 C., it lost its activity within fourteen days, but retained some of its activity for at least fourteen days when kept at 4 C.

AUTHORS' SUMMARIES.

THE CULTIVATION OF THE TYPHUS FEVER RICKETTSIA. C. NIGG and K. LANDSTEINER, J. Exper. Med. **55**:563, 1932.

Rickettsia prowazeki can be cultivated for many generations in vitro, without diminution in numbers or in virulence, in mediums similar to those described by

Maitland, Rivers and others for the cultivation of certain viruses. In all probability, such cultures can be maintained indefinitely. It has been impossible, thus far, to cultivate the rickettsia of typhus without employing living tissue.

AUTHORS' SUMMARY.

THE RELATIONSHIP OF PATHOGENIC BACTERIA TO UPPER RESPIRATORY DISEASE IN INFANTS. Y. KNEELAND, JR., and C. F. DAWES, J. Exper. Med. **55**:735, 1932.

Bacteriologic and clinical observations on respiratory disease in a semi-isolated infant population over a period of two years are recorded. In two severe winter outbreaks of respiratory infection, a parallel rise in the percentage of carriers of pathogenic organisms was noted. The first autumnal outbreak of colds seems to favor dissemination of the pathogenic organisms. The relationship of colds to the severer infections is roughly reciprocal. Infants between 8 and 14 months of age are subject to the most severe infections. The number of infants showing positive cutaneous reactions to products of pathogenic organisms increases during the winter months. The significance of these findings is discussed.

AUTHORS' SUMMARY.

THE RÔLE OF INTRACELLULAR BACTERIOPHAGE IN LYSIS OF SUSCEPTIBLE STAPHYLOCCCI. J. H. NORTHROP and A. P. KRUEGER, J. Gen. Physiol. **15**: 329, 1932.

The experiments described show that the significant condition for the occurrence of lysis is either a concentration of about 110 phage units inside each bacterium or of about 12×10^8 units in each millimeter of surrounding solution. Since these two quantities are always in constant ratio to each other, it is immaterial which one is used. Evidently, also, they cannot be distinguished by any experimental procedure carried out under equilibrium conditions. It is perhaps more reasonable to suppose that the internal phage is responsible for the reaction.

AUTHORS' SUMMARY.

VARIANTS OF BACTERIUM PARADYSENTERIAE AND BACTERIUM MORGANI. G. M. MACKENZIE and L. N. BATT, J. Immunol. **22**:257, 1932.

From a culture of B. paradysenteriae isolated during an epidemic two stable variants have been produced by growth in homologous immune serum broth. In colonial structure, sugar fermentations and agglutinative, agglutinogenic and agglutinin-absorption properties, the variants have shown distinct and persistent differences from the original culture. One variant, although forming granular emulsions, is inagglutinable both in homologous and in heterologous immune rabbit serum, nor does it absorb agglutinin from antiserum produced with the culture from which it was dissociated. The other variant has been shown to have lost an antigenic component present in the original culture, and to have acquired an antigenic component not present in the original culture. This variant has acquired an agglutinative component common to it and a culture of B. morgani. This culture of B. morgani has an agglutinative and agglutinin-absorbing component common to it and the paradysentery strain. These two components, one common to cultures of B. paradysenteriae and B. morgani and the other common to cultures of the variant and B. morgani appear to be different.

AUTHORS' SUMMARY.

THE ENCEPHALITOGENIC POWER OF VACCINIA VIRUS. R. THOMPSON and L. BUCHBINDER, J. Immunol. **22**: 267, 1932.

Presence or absence of the encephalitogenic property in various strains of the virus of vaccinia cannot be ascribed to heterogenetic origin, since derivants of the same strain differ in this respect. Variations in the character of the cutaneous

lesions produced by neurotropic and dermatropic viruses are apparently associated with presence or absence of the ability to produce encephalitis. Encephalitogenic strains are not obviously contaminated with herpes virus, since recovery from neurovaccinial infection affords as little immunity to herpes virus as does recovery from dermovaccinial infection. The power of neurotropic strains to produce encephalitis is not referable to contamination with the virus of poliomyelitis, since the latter virus does not cause a nonencephalitogenic strain of the virus of vaccinia to become encephalitogenic for rabbits. Evidence is presented which indicates that neurotropic strains are not contaminated by some unknown virus capable of producing encephalitis alone or when aided by vaccinial infection. The encephalitis-producing power of certain of the strains is probably a property of the virus. It is suggested that the presence or the absence of this property may be due to a process similar to that of dissociation in bacterial cultures.

AUTHORS' SUMMARY.

BACTERIAL ENDOTOXIN (IN SALMONELLA PULLORUM). J. H. HANKS and L. F. RETTGER, J. Immunol. **22**:283, 1932.

The cell bodies of cultures of S. pullorum contain, and by appropriate methods of extraction yield, a relatively heat-resistant poison which is highly toxic for rabbits and capable of killing guinea-pigs and mice. This toxin did not cause loss of weight or other noticeable symptoms of illness in chicks, regardless of the route by which it was introduced. The toxic principle was fairly stable in hydrogen ion concentrations ranging from p_H 3 to 12, and did not deteriorate during exposure to direct sunlight for twenty-four hours. It was destroyed by prolonged action of trypsin or of pepsin. It was not dialyzable through parchment bags, and could be precipitated with ammonium sulphate or acetic acid alcohol. When the toxin of S. pullorum was introduced into the skin of normal rabbits, the severity of the reaction was correlated with the toxicity of the same preparation for mice. Repeated injections of culture filtrate or of cellular antigen into rabbits gave rise to specific agglutinative antibodies and to nonspecific cutaneous hypersensitiveness. Immunization with toxin filtrate induced tolerance to the toxin, but did not afford protection against subsequent infection with live culture. It was impossible to demonstrate that growth or the production of toxin is materially increased under tensions of carbon dioxide and oxygen that approximate those of animal tissues. The disease caused by S. pullorum appears to be a septicemia, rather than a toxemia.

AUTHORS' SUMMARY.

Immunology

QUANTITATIVE STUDIES ON THE PRECIPITIN REACTION. M. HEIDELBERGER and F. E. KENDALL, J. Exper. Med. **55**:555, 1932.

A method, based on the precipitin reaction, is given for the microdetermination of the specific polysaccharide of the type III pneumococcus. As little as 0.01 mg. can be determined. The method should be applicable to any specific polysaccharide on standardization of a homologous antibody solution or antiserum in the region of excess antibody.

AUTHORS' SUMMARY.

REACTION OF RABBITS TO GREEN STREPTOCOCCI. M. P. SCHULTZ and H. F. SWIFT, J. Exper. Med. **55**:591, 1932.

Rabbits were rendered very hypersensitive by relatively small doses of green streptococci given intracutaneously, and somewhat less hypersensitive by similar doses of heat-killed vaccine prepared from hemolytic streptococci. Animals receiving the same doses intravenously gave, on subsequent testing, lesions slightly more marked than normal controls; but these lesions were qualitatively hard and nodular compared with the large, edematous lesions in the cutaneously sensitized group.

There was no parallelism between the degree of cutaneous or ophthalmic hypersensitivity and the agglutinin titer of the blood serum. Hypersensitivity to whole streptococci appears to depend more on previously induced focal infection than on circulating antibodies.

AUTHORS' SUMMARY.

SEROLOGY OF SYPHILIS: THE POSITIVE WASSERMANN REACTION IN NORMAL RABBITS. H. EAGLE, J. Exper. Med. **55**:667, 1932.

More than one half of normal rabbits contain complement-fixing or precipitating antibodies against Wassermann antigens (the alcohol-soluble lipoids of beef, rabbit and human hearts) by a sufficiently sensitive technic. Normal human serums tested by the same technic are uniformly negative. Intravenous injection of colloidal suspensions of the lipoids of beef and human hearts into rabbits occasionally causes a significant increase in the titer of this normal Wassermann (antilipoid) reaction. This may indicate a certain degree of antibody response to the lipoids as such; it may be due to the presence in such extracts of traces of foreign protein, which would activate the lipoid hapten into a complete antigen; or it may be a nonspecific increase in a normal antibody, not due to a specific antigenic stimulus. Confirming the results of Sachs, Klopstock and Weil, the addition of normal foreign (human) serum to the lipoids of rabbit, beef and human hearts makes them antigenic for rabbits. Intravenous injection of such lipoid-serum mixtures usually causes a significant increase in the titer of the complement-fixing and precipitating antibody against tissue lipoids. The precipitate that forms on the addition of tissue lipoids to human syphilitic serum is by far the most efficent antigen for the production, in rabbits, of antibodies to tissue lipoids that I have as yet encountered. Rabbits treated by intravenous injection of such a precipitate regularly present a Wassermann reaction the titer of which is many times higher than either that observed in human syphilis or that induced by the injection of a mixture of normal serum and lipoid. The marked antigenic property of the precipitate as compared with that of a mixture of normal serum and lipoid is considered to be due to the fact that it contains a foreign protein firmly bound to the lipoid particles, namely, the human reagin-globulin with which they have combined. This interpretation is supported by the observations that heating at 100 C., which does not affect the lipoid constituent of the precipitate, destroys its antigenic power for rabbits, and that a similar precipitate derived from Wassermann-positive rabbit serum instead of syphilitic human serum, and therefore containing tissue lipoid in combination with homologous (rabbit) protein, is completely nonantigenic for rabbits.

AUTHOR'S SUMMARY.

CHEMOIMMUNOLOGICAL STUDIES ON CONJUGATED CARBOHYDRATE-PROTEINS. O. T. AVERY, W. F. GOEBEL and F. H. BABERS, J. Exper. Med. **55**:761 and 769, 1932.

The synthesis of p-aminophenol α-glucoside has been described. This glucoside can be coupled to any protein to yield a synthetic α-glucoside-protein complex. A synthetic β-glucoside-protein complex has also been prepared. These synthetic sugar-protein complexes have been used as immunizing antigens in order to ascertain whether α-glucosidic and β-glucosidic unions influence the specificity of the immune response in animals.

In the case of the synthetic antigens containing the A and B compounds of dextrose (glucose) alone, the evidence indicates that the immunologic relationships of the reactive glucosides are determined by known variations in their chemical constitution and are independent of the protein to which they are attached. In view of these findings it seems not unlikely that in the case of the polysaccharides, because of their more complicated structure and the greater possibility for variation in molecular configuration, there may be found many examples of a similar overlapping specificity among carbohydrates of unrelated origin.

AUTHORS' SUMMARIES.

THE SEROLOGICAL SPECIFICITY OF PEPTIDES. K. LANDSTEINER and J. VAN DER SCHEER, J. Exper. Med. **55**:781, 1932.

With the idea that studies on the serologic properties of peptides may ultimately aid in the understanding of the precipitin reactions of proteins, antigens have been prepared containing aminobenzoylated dipeptides, namely glycylglycine, glycyl-d-l-leucine, d-l-leucyl-glycine and d-l-leucyl-d-l-leucine. These four antigens were found to be different serologically, their specificity depending on the structure of the terminal amino-acid carrying the free carboxyl group, and to a less degree also on the second amino-acid. The results were obtained by means of precipitin and inhibition tests. Analogies to observations on the specificity of enzymes are discussed.

AUTHORS' SUMMARY.

THE RELATION OF HYPERSENSITIVENESS TO LESIONS IN THE LUNGS OF RABBITS INFECTED WITH PNEUMOCOCCI. L. A. JULIANELLE and C. P. RHOADS, J. Exper. Med. **55**:797, 1932.

Intratracheal injection of egg albumin or pneumococcic protein into rabbits previously inoculated with the respective antigen induces an inflammatory reaction in the lungs. A similar reaction occurs following intratracheal injection of pneumococcic protein into rabbits previously inoculated with heat-killed suspensions of the bacteria. This reaction appears to be related to the presence of circulating antibody and to have the nature of the Arthus reaction. A study of the reactions of the lungs of rabbits to infection caused by intravenous injections of pneumococci reveals that reactions occur irregularly in the lungs; in the lungs in which they occur, the histologic changes are not different as between normal rabbits and rabbits made resistant by previous intravenous or intracutaneous injections of pneumococci. Intratracheal injection of pneumococcic protein followed by intravenous injection of virulent pneumococci on the next day does not alter the course and character of the infection in resistant rabbits. The experiments reported in this paper bring no evidence to support the view that the lesions in the lungs of rabbits following intravenous injection of pneumococci are modified by any previous state of sensitivity.

AUTHORS' SUMMARY.

ANTIBODIES AGAINST VACCINIA VIRUS. R. THOMPSON, E. L. HAZEN and L. BUCHBINDER, J. Immunol. **22**:189, 1932.

Serums from rabbits hyperimmunized by intravenous and intraperitoneal injections of tissues (brain, testicle and skin) containing vaccinial virus caused fixation of alexin in the presence of a suitable dilution of vaccinial brain or skin suspension, but not in the presence of nonvaccinial tissue suspensions. The evidence indicates that this fixation is a process specific for tissue containing vaccinial virus, regardless of the tissue in which the virus is propagated, and that it is not due to the immune reactions of concomitant bacteria.

AUTHORS' SUMMARY.

NATURAL AGGLUTININS AND THEIR RELATIONSHIP TO THE SOMATIC AND FLAGELLAR ANTIGENS OF BACTERIA. H. J. GIBSON, J. Immunol. **22**:211, 1932.

Normal serum from various mammalian animals contains agglutinins that react with the H and O antigenic constituents of many bacteria. Flagellar suspensions have been used to demonstrate H-agglutinins. Agglutinin-absorption experiments show that the specificity of natural agglutinins (as described in a previous communication) depends chiefly on the H type. The O type appears to possess affinities for antigenic constituents that are more widely shared by different organisms. It was not found possible to demonstrate the antigenic relationship among members of the Salmonella and Bacillus proteus X groups so precisely with normal serums as with immune serums. The thermolability of the O type of agglutinins was found to be greater than that of the H type in the normal serum of a number

of animal species. Both showed greater lability than the corresponding immune agglutinins. Rough and smooth variants of the same bacterial strain showed antigenic differences in their reactions with normal serums.

AUTHOR'S SUMMARY.

ELECTRIC CHARGE OF BACTERIAL ANTIGENS. L. OLITZKI, J. Immunol. **22**:251, 1932.

The H-antigen of B. proteus X19 carries a negative electric charge over a p_H range of from 12 to 4.4; the O-antigen, over a range of from 12 to 3.4. By cataphoresis of whole bacteria at p_H 4, it is possible to obtain large amounts of pure O-antigen at the positive pole of the apparatus. By cataphoresis of bacterial extracts at p_H 4, it is possible to remove the O-antigen completely, leaving pure H-antigen in the middle vessel of the apparatus.

AUTHOR'S SUMMARY.

SKIN REACTIONS TO HUMAN AND AVIAN TUBERCULIN IN DISEASES OF LYMPHOID AND MYELOID TISSUE. F. PARKER, JR., H. JACKSON, JR., G. FITZ HUGH and T. D. SPIES, J. Immunol. **22**:277, 1932.

Tuberculin tests with both human and avian tuberculin were carried out on patients with Hodgkin's disease, malignant lymphoma, leukemia, pernicious anemia and cancer. Similar tests were done on tuberculous and normal persons. Fewer positive reactions were obtained in the patients with diseases of the lymphoid and myeloid tissues and those with malignant disease than in normal persons and tuberculous patients. More positive reactions to avian than to human tuberculin were found, except in the normal group.

AUTHORS' SUMMARY.

PROGRESSIVE, SELECTIVE ABSORPTION OF PRECIPITINS IN MULTIVALENT SERUM. L. HEKTOEN and E. DELVES, J. Infect. Dis. **50**:237, 1932.

Precipitins in multivalent serum may be removed successively with reasonable success by the selective action of single antigens.

AUTHORS' SUMMARY.

FLOCCULATION TESTS FOR THE DIFFERENTIAL DIAGNOSIS OF SMALLPOX AND CHICKENPOX. L. C. HAVENS and C. R. MAYFIELD, J. Infect. Dis. **50**:242, 1932.

Flocculation tests with thirty-eight specimens of serum in thirty-five cases of smallpox gave positive results with all but five. Four of the negative specimens were taken during the first week of the disease. Two cases in which successive specimens were obtained showed an increase in titer during the course of the disease. Eight specimens of serum in seven cases of chickenpox gave negative results. Flocculation tests with smallpox scabs and immune rabbit serum gave definitely positive results with dilutions of the antigens as high as 1:2,000. Chickenpox scabs invariably failed to flocculate in dilutions higher than 1:500. The flocculation obtained with lower dilutions of the chickenpox antigens occurred also with normal rabbit serum, and its nonspecific character was further demonstrated by absorption of the serum with staphylococci present in the scabs.

AUTHORS' SUMMARY.

PROTEINS OF RAGWEED POLLENS. C. A. JOHNSON and B. Z. RAPPAPORT, J. Infect. Dis. **50**:290, 1932.

Patients with autumnal hay fever do not react alike to the water-soluble protein fractions of giant and short ragweed pollens obtained by precipitation at various concentrations of ammonium sulphate. Rabbits treated with these preparations produced precipitins that reacted not only with the two ragweeds mentioned, but

also with extracts of rough marsh elder. Southern ragweed, cocklebur, slender ragweed, Western ragweed and bur ragweed.

Thirty-six patients subject to autumnal hay fever were tested by the cutaneous method with extracts of all of these pollens diluted to the same concentration of nitrogen. All reacted to short ragweed, thirty-five to giant ragweed, thirty-four to Western ragweed, thirty-three to slender ragweed, thirty-three to cocklebur, thirty to Southern ragweed and twenty-four to rough marsh elder. The short and giant ragweeds produced the largest, and the rough marsh elder, the smallest wheals. Immunologically, it would appear that these pollens are closely related; clinically, without attempting to explain differences in sensitivity in individual patients, the relationship is also apparent. While the data obtained from experments on animals may be significant, we do not wish to imply that they are necessarily applicable to the symptom complex of hay fever. From evidence presented it would seem that the active principle of ragweed pollen is of protein nature, or that it clings to a protein moiety. A nitrogen-containing lipoid was obtained from ragweed pollen by ether extraction, which gave distinctly positive reactions by the intradermal method in nineteen of twenty-one patients with autumnal hay fever. Other minor fractions of ragweed pollen are relatively inert.

C. A. JOHNSON.

THE STANDARDIZATION OF ANTIMENINGOCOCCIC SERUM BY THE POLYSACCHARIDE PRECIPITIN TEST. J. ZOZAYA, J. Infect. Dis. **50**:310, 1932.

This method of standardizing antimeningococcic serum gives direct evidence of the probable protective value of a given serum. Further clinical evidence is necessary to establish this assumption definitely. The agglutination test should, for the present, be continued with the object of determining the polyvalency of the serum, but not with that of judging its potency. Further work with the complex meningococcic polysaccharide may result in finding a fraction which is type-specific, and which can be substituted for the group-specific carbohydrate. Attempts are now being made to carry on this fractionation, as well as to determine the chemical composition of the complex group carbohydrate. This simple method should be given a thorough trial. Comparisons on a therapeutic basis should be made with serums containing different values of polysaccharide precipitable substance or unit value per cubic centimeter. Unfortunately, there is not a method at hand to test potency on animals, although the method suggested by Schwartzman may be of use in preliminary tests for comparison. The therapeutic dosage in terms of units would have to be established by experience, as is being done with the antipneumococcic serum. An advantage of this method is the constant control of the standard serum that can be supplied from Washington, for one can dilute or concentrate a given serum to give exactly the titration desired.

AUTHOR'S SUMMARY.

THE LEUKOCYTE RESPONSE IN MAN TO DICK TOXIN, WITH SPECIAL REFERENCE TO EOSINOPHIL CHANGES. S. L. VAUGHAN, J. Infect. Dis. **50**:315, 1932.

The eosinophil reaction had no apparent relation to the intensity of the Dick cutaneous reaction, to the rash or to the history of an attack of scarlet fever.

AUTHOR'S SUMMARY.

THE ANTIGENIC PROPERTIES OF RABIES VIRUS. L. C. HAVENS and C. R. MAYFIELD, J. Infect. Dis. **50**:367, 1932.

Specific flocculation of rabies virus occurs in appropriate dilutions of immune rabbit and guinea-pig serum. Flocculation occurs with fixed virus (rabbit brain) and with street virus. The serum of the rabies-immune guinea-pigs has been shown to possess specific complement-fixing antibodies for rabies virus. Immune rabbit serum is unsatisfactory for complement-fixation experiments with viruses, because of its anticomplementary nature.

AUTHORS' SUMMARY.

SOLUBLE SPECIFIC SUBSTANCES FROM YEASTLIKE FUNGI. H. D. KESTEN and E. MOTT, J. Infect. Dis. **50**:459, 1932.

A soluble polysaccharide fraction has been prepared from each of ten yeast-like fungi. Antiserums prepared against these fungi cause precipitation in high dilutions of the homologous soluble substances. In addition, cross-precipitin reactions are common. By absorption of precipitin on the mycotic bodies, however, the soluble substances exhibit definite specificity. Those obtained from Saccharomyces, Willia and Monilia parapsilosis are distinct among themselves and also from the remainder of those studied. The soluble substances from Monilia albicans, Monilia psilosis and Endomyces albicans, however, are serologically similar. This similarity is additional evidence for considering these as merely strains of a single species, M. albicans.

AUTHORS' SUMMARY.

THE RETICULO-ENDOTHELIAL APPARATUS IN INFECTIOUS DISEASES. K. M. DWOLAIZKAYA-BARYSCHEWA and N. W. KAGAN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:429, 1932.

The reticulo-endothelial system was eliminated by splenectomy and by blockade. The portal of entrance of B. typhosus and B. paratyphosus B had a distinct influence on the activity of the reticulo-endothelial system: in infections per os its defensive action is very insignificant, but becomes pronounced in subcutaneous infections.

I. DAVIDSOHN.

THE DEPENDENCE OF THE THERAPEUTIC EFFECT OF IMMUNE SERUMS ON THE INTACT RETICULO-ENDOTHELIAL SYSTEM. I. L. KRITSCHEWSKI, P. L. RUBINSTEIN and E. S. HERONIMUS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:463, 1932.

The full therapeutic effect of tetanus antitoxin and antipneumococcus serum was obtained only in healthy mice, while animals in which the reticulo-endothelial system was damaged by splenectomy and injections of certain colloids were not protected against injections of tetanus toxin and of pneumococci, type I.

I. DAVIDSOHN.

THE SPIROCHAETA PALLIDA REACTION AND ITS RELATION TO THE WASSERMANN REACTION. W. GAEHTGENS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:527, 1932.

Because of its high sensitivity and specificity, an aqueous phenolized suspension of cultures of Spirochaeta pallida is recommended for the complement-fixation test for syphilis. Technical details of the test are given. Positive syphilitic serums contain at least two different types of reacting substances, as shown by proper absorption experiments: (*a*) those reacting with the Spirochaeta pallida antigen, and (*b*) those reacting with syphilitic liver. The Wassermann reaction and the Spirochaeta pallida reaction rest on two basically different serologic phenomena.

I. DAVIDSOHN.

Tumors

THE ASSOCIATION OF TUBERCULOSIS AND CARCINOMA. F. G. COOPER, Am. Rev. Tuberc. **25**:108, 1932.

Several hundred reports of cases in which carcinoma and tuberculosis were present in the same organ are reviewed. In addition, twenty-four new cases are presented. All these revealed an intimate association of malignant growth and tuberculous lesion. Cooper concludes that the two diseases are not antagonistic. Tuberculosis may exist with tumors of all degrees of malignancy. Tuberculosis in an organ or biopsy specimen does not exclude the possibility of malignant tumor.

H. J. CORPER.

THE CLINICAL SIGNIFICANCE AND APPLICATION OF HISTOLOGIC GRADING OF CANCERS. W. C. HUEPER, Ann. Surg. **95**:321, 1932.

Sections removed for grading of malignancy must be taken from the peripheral zone of the tumor, must be properly prepared and stained, and must be evaluated by a pathologist familiar with the method of grading. Grading is helpful in the selection of the type of treatment. The grade must never interfere with the extent of the intensity of treatment. The grade indicates the proliferative and metastatic tendencies. A reliable prognostication must include consideration of at least three factors: the grade of malignancy, the extent and the location of the tumor.

AUTHOR'S SUMMARY.

THE BASOPHIL ADENOMAS OF THE PITUITARY BODY AND THEIR CLINICAL MANIFESTATIONS (PITUITARY BASOPHILISM). H. CUSHING, Bull. Johns Hopkins Hosp. **50**:137, 1932.

Of all subjects that engage the attention of the profession at the present day, that of endocrinology particularly lends itself to the temptation of impressionistic speculation. During the past ten years, innumerable syndromes of so-called polyglandular type, some of them bearing a certain resemblance to that under consideration, have often been described in print. Examples of "diabetes in bearded women," of rapidly acquired obesity, of hypertension, of masculinization in the female and of sexual precocity in children of either sex, often associated with hyperplasias or tumors of one sort or another of the suprarenal glands, have been so many and varied as to baffle analysis. Some of these syndromes have unquestionably been due to corticosuprarenal tumors, and in not a few instances, indeed, such a tumor has been removed at operation with definite amelioration of symptoms. What is more, in similar states suprarenal tumors have been found after death in the absence of any recognizable abnormality in the pituitary body, though all too often the protocol refers to the examination of this structure either in the briefest terms or not at all. While there is every reason to concede, therefore, that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal or with suprarenal tumors, the fact that the peculiar polyglandular syndrome, which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the suprarenal cortex other than a possible secondary hyperplasia will give pathologists reason in the future more carefully to scrutinize the anterior lobe of the pituitary gland for lesions of similar composition.

AUTHOR'S SUMMARY.

INACTIVATION OF AGENT OF A CHICKEN TUMOR BY MONOCHROMATIC ULTRAVIOLET LIGHT. E. STURM, F. L. GATES and J. B. MURPHY, J. Exper. Med. **55**:441, 1932.

Even though part of the energy of the incident light is probably absorbed by chemical entities that play no part in the specific reaction of inactivation, nevertheless the wavelengths most active in destroying biologic cells or agents will presumably be among those absorbed in the highest proportion. This would indicate that the curves here presented are approximately reciprocal to the coefficients of absorption of particular substances, the destruction of which caused the inactivation of the agents or the death of the cells. The similarity between the curves for bacteria, virus and phage, both in shape and in total involved energies, suggests the presence of a common factor, or of closely related chemical entities, sensitive to ultraviolet rays, whereas the data for the tumor agent suggest that its inactivation is due to the destruction of a substance having an essentially different spectral absorption, and therefore of a different chemical character. While the amount of ultraviolet energy required to affect the tumor agent is great, it is

still less than that involved in the inactivation of some of the enzymes. A study is under way to compare the deduced spectral analysis with the actual coefficients of absorption of the highly purified tumor agent.

AUTHORS' SUMMARY.

EFFECT OF TESTICLE EXTRACT ON TRANSPLANTABLE MOUSE TUMORS. R. C. TANZER, J. Exper. Med. **55**:455, 1932.

Grafts of a transplantable mouse sarcoma designated as no. 180, and those of an attenuated strain of a more malignant sarcoma, S/37, treated with testicle extract, either fail to grow on inoculation or result in tumors of a lower rate of growth than that of the controls. Autografts of spontaneous mouse tumors so treated show little if any effect, while the Bashford adenocarcinoma and the unattenuated S/37 are unaffected. The factor in testicle extract responsible for the retarding activity passes readily through a Berkefeld filter and is thermostable.

AUTHOR'S SUMMARY.

PRIMARY ADENOCARCINOMA IN A MECKEL'S DIVERTICULUM. P. MICHAEL and H. G. BELL, Surg., Gynec. & Obst. **54**:95, 1932.

A primary adenocarcinoma in a Meckel's diverticulum, apparently the first to be reported, is described in a man 67 years of age. Seven instances of sarcoma of Meckel's diverticulum have been reported.

AUTOLYSIS IN MALIGNANT AND NORMAL RABBIT TISSUES. H. I. PRICE, Biochem. J. **25**:1491, 1931.

Robin, in an analysis of the composition of a series of tissues obtained at autopsy from persons with and without malignant tumors (*Bull. Acad. de méd., Paris* **81**:799, 1919), came to the conclusion that the proportion of hydrolyzed to unhydrolized protein was greater in the tissue adjacent to a malignant growth than in the growth itself or in the corresponding tissue of a normal person. Price repeated Robin's experiment, using rabbits inoculated with the Brown-Pearce tumor and having metastases in the liver and kidneys. Determinations of hydrolyzed and unhydrolyzed protein content, and of water content, were made on the tumor tissue, the adjacent normal tissue and distant normal tissue from the same organ, at intervals up to twenty-four hours from the moment of death. The highest proportion of hydrolyzed to unhydrolyzed protein, at the instant of death, was present in the tumor tissue, the lowest in the tissue most distant from the malignant growth. As the result of a gradual postmortem transfer of water, presumably containing dissolved, hydrolyzed protein, from the tumor area to the surrounding normal tissue, the proportion of hydrolyzed to unhydrolyzed protein in the tissue adjacent to the tumor gradually approached and finally exceeded that of the tumor itself (the balance observed by Robin). The tissue adjacent to the tumors contained a definitely higher proportion of hydrolyzed to unhydrolyzed protein than the tissue more distant from the tumors, during the entire interval of observation. No evidence was found, however, to support Robin's earlier conclusions that the tissues adjacent to a malignant growth may autolyze more rapidly than the corresponding tissues of a noncancerous person, and that the protein requirements of a tumor are met by the hydrolysis of the proteins of the surrounding tissue. The increased proportion of hydrolyzed protein in the tissues adjacent to a tumor may be absorbed from the disintegrating tumor tissue rather than vice versa.

ARTHUR LOCKE.

THE PHOSPHATIDE AND CHOLESTEROL CONTENTS OF NORMAL AND MALIGNANT HUMAN TISSUES. M. JOWETT, Biochem. J. **25**:1991, 1931.

Tumor tissues have a higher phosphatide and cholesterol content, and a higher phosphatide-cholesterol ratio, than the tissues in which they have their origin.

ARTHUR LOCKE.

DISEASE IN MICE TREATED WITH CARCINOGENIC AGENTS. J. M. and C. C. TWORT, J. Path. & Bact. **35**:219, 1932.

This article, which will be of special interest to workers using mice in cancer research, gives a review of the results of some 12,000 postmortem examinations of mice treated with carcinogenic and other agents.

PARATHYROID TUMORS WITHOUT OSTEITIS FIBROSA. C. HADFIELD and H. ROGERS, J. Path. & Bact. **35**:259, 1932.

Two instances of large parathyroid adenoma are described, in one of which there was a normal skeleton, while in the other there was acromegaly associated with a large chromophil adenoma of the pituitary gland. These cases, as well as three others from the literature, illustrate the fact that a parathyroid tumor, closely resembling the normal gland in structure, may occur without elaborating any excess of internal secretion.

CARCINOMA OF THE PITUITARY GLAND WITH ABDOMINAL METASTASES. M. D. GILMOUR, J. Path. & Bact. **35**:265, 1932.

Gilmour reports a case of adenocarcinoma of the pituitary gland with multiple metastases. Lesions in the thyroid gland and ovary are described, and it is considered that these lesions and the pituitary disease are interrelated.

IMMUNITY TO JENSEN'S RAT SARCOMA PRODUCED BY TUMOUR EXTRACTS. H. CHAMBERS and G. M. SCOTT, J. Path. & Bact. **35**:283, 1932.

Experiments are described which show that Jensen's rat sarcoma, deprived of its blood supply and kept at blood temperature, undergoes a transitory change during which extracts from it have immunizing properties. The immunizing property develops for a short time with increasing potency and then disappears; it is apparently due to changes in the tumor cells set up by defective oxygenation.

AUTHORS' SUMMARY.

THE CLASSIFICATION OF CANCER OF THE RECTUM. C. E. DUKES, J. Path. & Bact. **35**:323, 1932.

Cancers of the rectum can be divided into *A*, *B* and *C* cases according to the extent of spread. *A* cases are those in which the growth is limited to the wall of the rectum; *B* cases, those in which there is extrarectal spread but no lymphatic metastases; *C* cases, those in which metastases are present in the regional lymph nodes. A striking difference is found in the operative mortality and in the period of survival after operation in these three groups. There is reason to believe that in *A* cases the disease is completely eradicated by rectal excision, and the excellent results of operative treatment confirm the opinion previously expressed that lymphatic metastases are not found until a rectal carcinoma has spread by direct continuity to the extrarectal tissues. A good prognosis is justified also in *B* cases, though slightly less favorable than in *A*. The results of surgical treatment in *C* cases are disappointing. The scope and limitations of histologic grading by Broders' method are discussed, and the conclusion is reached that grading of a tumor is also of value for prognosis, though not when applied to fragments removed for diagnosis.

AUTHOR'S SUMMARY.

A MALIGNANT MELANOTIC TUMOUR OF GANGLION CELLS ARISING FROM A THORACIC SYMPATHETIC GANGLION. W. G. MILLAR, J. Path. & Bact. **35**:351, 1932.

A case is described of a very malignant tumor composed of cells of nervous origin the structure of which approximated, in a greater or lesser degree, that of ganglion cells. The more highly differentiated ganglion cells were loaded with

pigment; this was melanin and was present in sufficient quantity to make parts of the tumor as black as an ordinary cutaneous melanoma. Evidence is adduced that the tumor arose from nerve cells in the seventh left thoracic sympathetic ganglion. In view of the undoubted nervous origin of this tumor it is both possible and likely that a similar origin can be postulated for some at least of the melanomas arising in the suprarenal medulla.

AUTHOR'S SUMMARY.

Medicolegal Pathology

LETHAL ACCIDENT DUE TO INHALATION OF TRICHLORETHYLENE. R. PFREIMBTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:339, 1931.

The now frequent use of trichlorethylene ($CHCl:CCl_2$), instead of benzene, for cleaning metal or for extraction of fat substances has led to fatal poisonings; twenty-four such instances have been reported. A case involving an 18 year old mechanic is described. Autopsy showed vesicle-like formations in the skin of the lower parts of the arms and legs with a marginal zone of hyperemia, presenting a burnlike effect. On slicing the brain, a sweetish odor, similar to that of chloroform, was noticed. Death occurred from asphyxiation due to aspiration of the gastric contents into the respiratory system while vomiting during unconsciousness. The liver showed toxic changes of the hepatic cells and deposits of pigments due to blood lysis. Eosinophils were increased in number in the peripheral blood. This case illustrates the danger of inhalation of trichlorethylene, even in a cool room where the oxygen content of the air is sufficient. In prolonged exposures, it might cause partial blindness from degenerative changes of the optic nerve and also damages to the sensory branches of the trigeminus. The chronic use of this drug may lead to acute yellow atrophy of the liver.

E. L. MILOSLAVICH.

AN ERRONEOUSLY INTERPRETED GUNSHOT WOUND OF THE SKULL. K. WALCHER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:345, 1931.

While riding on a motorcycle, a man was shot in the back of the head, with the outlet in the frontal region and extensive fracturing of the skull. Both wounds, entrance and exit, were irregular and led the examiners to assume erroneously that the inlet was in the right temporal region. The assailant pleaded self-defense, which was refuted later on by the subsequent correct anatomic interpretation of the wounds as having been produced by discharge of a gun from behind, at close range.

E. L. MILOSLAVICH.

CHEMICAL ANALYSIS OF GUNSHOT WOUNDS. O. SCHMIDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:353, 1931.

In examining a gunshot injury, one should first remove the visible unburnt particles of powder and subject them to the diphenylamine sulphuric acid test. A positive reaction alone might prove that a pistol was fired at close range. However, should the results be doubtful or should there be question as to the character and type of the bullet or uncertainty as to whether the perforation is the inlet or the outlet wound, chemical examinations are instituted. The ring of contusion must be examined separately. Presence of minute traces of metallic particles farther away from the bullet wound means a shot fired at close range; consequently it indicates the entrance of the bullet. If the inlet and outlet wounds disclose presence of lead, a lead bullet was used. Absence of any lead proves penetration by a jacketed projectile. If the latter, however, was smashed into small pieces, such fragments may leave traces of lead in the exit wound. Evidence of lead and mercury in the ring of contusion in wounds produced by discharge of a gun at a great distance indicates use of Flobert ammunition, and the site of deposits of mercury points to the entrance of the discharge. In chemical examina-

tions of gunshot perforations of clothing for antimony, one should keep in mind that antimony is used in the textile industry for preparation of fabrics, and therefore control tests should not be omitted.

E. L. MILOSLAVICH.

SPERM CRYSTALS. E. ZIEMKE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:367, 1931.

The most commonly used tests in examinations for sperm are the Florence iodine reaction and the Barberio trinitrophenol test. Niederland (*Med. Welt* **5**:149, 1931) recently described a new microchemical reaction: If sulphuric acid is added to a drop of sperm, numerous crystals in the form of prismatic needles or rods soon develop and can be observed by the naked eye or by help of a magnifying glass. The crystals are insoluble in cold or warm water, ether, alcohol or chloroform. In testing for sperm on clothing, the spot is macerated in water for from three to four hours. To a drop of the extract on a slide one drop of a 3 per cent solution of sulphuric acid is added. The crystals develop after a few minutes; in very thin extracts, after a few hours. The formed crystals remain unchanged for several months. The crystals can be obtained even from disintegrated sperm, when the Florence and Barberio reactions usually fail to show any results. Other bodily fluids and secretions, such as nasal mucus, sputum, gonorrheal pus and vaginal secretion, yield a positive sulphuric acid reaction, but the results of the Florence and Barberio tests in these cases are always negative. Experiments made with these three tests disclosed that the Niederland reaction is the most reliable one, while the Florence test gave results in 70 per cent of the cases examined and the Barberio test in only 26.3 per cent. The ready development of the crystals, which consist of calcium phosphate, by application of sulphuric acid is explained by the abundant calcium content of sperm. If one adds a 3 per cent solution of sulphuric acid to a solution of calcium chlorate, the same kind of crystals results. Sperm contains in 900 parts of water, 100 parts of solid material, of which 60 parts are organic and 40 inorganic substances. In the last mentioned, 30 parts are represented by calcium phosphate. The practical value of this test is limited, since all the fluids and secretions containing calcium give the same result. But an absence of the sulphuric acid reaction positively eliminates presence of sperm. Should the reaction yield a positive result, a subsequent examination of the rest of the same material with the Florence test should follow. The Niederland test is an important addition to the already existing sperm reactions and serves as a general, reliable orientation, but cannot replace the Florence test.

E. L. MILOSLAVICH.

TANGENTIAL GUNSHOT WOUNDS OF THE SKULL. R. M. MAYER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:419, 1932.

Atypical gunshot wounds result if a projectile strikes the convexity of the skull in a slanting direction. Thus the external and internal tables become irregularly fractured and detached, and the tiny fragments of bone appear raised. From the perforation made by the bullet, fracture lines extend in radial or star-shaped fashion. The angle at which the bullet penetrated can be reconstructed from the slope of the edge of the wound. However, one has to consider the position of the body or of the head at the time of the discharge of the pistol, and also the possibility that the bullet might have been deflected from its course, striking the skull transversally.

E. L. MILOSLAVICH.

SPONTANEOUS COMBUSTION OF THE HUMAN BODY. ERNST DARMSTAEDTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:437, 1932.

This is a critical review of the literature of the last century, with a discussion of the physicochemical problems involved. The article, which is of historical interest, should be read in the original.

E. L. MILOSLAVICH.

Book Reviews

Antony van Leeuwenhoek and His "Little Animals." Being Some Account of the Father of Protozoology and Bacteriology and His Multifarious Discoveries in These Disciplines. Collected, Translated and Edited From His Printed Works, Unpublished Manuscripts and Contemporary Records by Clifford Dobell, F.R.S., Protistologist to the Medical Research Council, London; Foreign Member of the R. Accademia dei Lincei, Rome; Sometime Fellow of Trinity College, Cambridge. Published on the Three Hundredth Anniversary of His Birth [Oct. 24, 1632]. Pp. 435, with 32 plates. Price, $7.50. New York: Harcourt, Brace and Company, 1932.

This remarkable book begins with an epistle to the reader in which the author explains how the book came to be written. "It is now some 25 years since I first began to try and find out something about Leeuwenhoek and his discoveries in protozoology and bacteriology. The task has always been hard, but because of my personal interest it has never been irksome. My interest has, indeed, grown with my knowledge, and the more I have found out, the more I have ever wanted to find out about this truly marvelous man and his works. From the very beginning, I have been able to get little or no help from the writings of others (most of whom merely led me astray), so that I have always had to do the best I could for myself." After many setbacks, Dobell found that all of Leeuwenhoek's original writings were in the form of letters in colloquial Dutch, and that these letters for the most part are extant in the archives of the Royal Society in London. Now followed years of effort to learn to read Leeuwenhoek's script before the contents of the letters could be mastered. In studying the numerous letters much was learned about the man himself, his character and his work in general. Apparently search has been made also of every other accessible source of information, and the result is an account of surpassing interest of the life of Leeuwenhoek and his work in protozoology and bacteriology. It is obvious, as the author himself points out, that the making of this book has been a labor of love.

The account of Leeuwenhoek's life occupies pages 19 to 105. Aside from his apprenticeship of six years to a draper in Amsterdam his days were spent in Delft, where he died in 1723, at more than 90 years of age. In 1654 he set himself up as draper and haberdasher. Plate V is a facsimile bill in Leeuwenhoek's writing. He had no formal, higher education. He had not, as is sometimes stated, any sort of medical or scientific training. He knew only one language, the Dutch of his time, in which he expressed himself in simple fashion. In 1673, apparently without any warning, he offered a letter for publication in the transactions of the Royal Society of London. This letter dealt with microscopic observations on mold, on the bee and on the louse. Dobell tells us that this letter was sent at the instance of Régnér de Graaf, of graafian follicle fame, a friend and fellow-townsman of Leeuwenhoek, and one of the many correspondents of the energetic Henry Oldenburg, the first secretary of the Royal Society. From this time on until his death, fifty years later, Leeuwenhoek sent letters to the Royal Society, which "cover an immense field, and contain observations on matters zoological, botanical, physical, physiological, and miscellaneous (unclassifiable). They are mostly—but not entirely—concerned with observations and discoveries made with the microscope." Even on his death bed he sent two letters. In 1680 Leeuwenhoek was made a member of the Royal Society. His observations were made by means of microscopic lenses of his own making. He left behind him about two hundred and forty-seven microscopes. He worked entirely by himself. How he succeeded in seeing what he described in his letters is a mystery, toward the solution of which Dobell offers pertinent suggestions. All these matters and much more—his visitors, the impression that he made on his contemporaries, the devotion of his daughter,

Maria, the various translations and publications of his letters (he wrote no books or formal papers), his health, etc.—are set forth with abundant documentation in the light of the history of his own time. On one weighty point the chronicle is silent, namely: Just how did it happen that Leeuwenhoek began to grind lenses and make observations with his microscopes? All that can be said in answer is that he worked in response to a craving after knowledge. How the start was made and why is not known.

Pages 102 to 299 contain, with comments and annotations, the translations into English by Dobell of Leeuwenhoek's original letters in Dutch, in which are recorded his observations on "little animals"—protozoa and bacteria, free-living as well as entozoic. Facsimiles are given of parts of these letters. In the translation an effort was made to preserve the flavor of Leeuwenhoek's writing and to meet also the requirements of modern protistology. One example, chosen at random, may be given: In letter 110, in the midst of a discussion of the eggs of snails, the germination of wheat and the spat of oysters, Leeuwenhoek wrote that he mixed stuff from the hollows in the roots of one of his teeth, which he had removed because it was loose, "with clean rain-water and set it before my magnifying-glass so as to see if there were as many living creatures in it as I had aforetime discovered in such material: and I must confess that the whole stuff seemed to me to be alive. But notwithstanding the number of these animalcules was so extraordinarily great (though they were so little withal, that 'twould take a thousand million of some of 'em to make up the bulk of a coarse sand-grain, and several thousands were a-swimming in a quantity of water that was no bigger than a coarse sand-grain is), yet their number appeared even greater than it really was: because the animalcules, with their strong swimming through the water, put many little particles which had no life in them into like motion, so that many people might well have taken these particles for living creatures too." It will be sufficient to say further that after years of patient labor Leeuwenhoek's descriptions of protozoa and bacteria now have been rendered into English by a scientist and scholar of unique competence for the task. It is astonishing how many microbic forms Leeuwenhoek described so clearly that they can be recognized today. It is noteworthy also that he confined himself to plain, objective descriptions without speculation, and that he did not associate his "little animals" with the causation of disease.

The next sixty pages deal with elucidations and annotations concerning various topics: Leeuwenhoek's name, his language, his microscopes and microscopic methods, his dwelling, his draughtsmen, his portraits, his seals and his "first 27 unpublished letters." These letters were regarded as lost, but most of them have been found by Dobell among the manuscripts in the Royal Society.

In his envoy Dobell discusses comprehensively and critically Leeuwenhoek's place in protozoology and bacteriology. Before Leeuwenhoek there was speculation and prophecy only in regard to microbes; before him nobody saw a protozoon or a bacterium with his own eyes; consequently he alone is entitled to the distinction of being called the father of protozoology and bacteriology. "Leeuwenhoek will be finally judged by his own writings, and not by anything that other people say he wrote. He has left us a great mass of records—both published and unpublished—from which we can now extract what we please. I have endeavored to recover from them all his observations on the Protozoa and the Bacteria, and to set in order his inchoate and uncorrelated findings in a manner which may fairly convey their import and importance to present-day students. To me his words, when judicially weighed in the scales of contemporary and recent knowledge, prove conclusively that he was the first protozoologist and the first bacteriologist."

The volume, an admirable and attractive example of appropriate bookmaking, concludes with a short list of Leeuwenhoek's writings—manuscripts and publications—a list of other references and sources and an index.

Dobell has made an important addition to the history of science. We have only a few books about scientific men and their work as interesting as his book about Leeuwenhoek.

Classic Descriptions of Disease. By Ralph H. Major, M.D., Professor of Medicine, University of Kansas School of Medicine. Price, $4.50. Pp. 630, with 130 illustrations. Springfield: Charles C. Thomas, 1932.

This interesting book is a sister volume to Long's "Readings in Pathology" and to Fulton's "Selected Readings in the History of Physiology." It was a happy idea that led the editor to gather the selections and arrange them for publication, which has been carried out commendably by the publisher. The book contains selected original descriptions of disease from Hippocrates down to the present day, with brief historical summaries and biographic sketches by the editor. It is essentially an anthology of nosography. There are reproductions of portraits, many unusual, of title and text pages of old books, and of drawings and apparatus. In all there are 376 selections from 179 writers of outstanding contributions to the knowledge of disease. Of the nonmedical writings included may be mentioned accounts by Boccaccio, Kircher and Defoe of the plague. American medicine is well represented. No fault may be found with the selections, and the field has by no means been exhausted. Treatment has not been included; neurology, ophthalmology, dermatology and other special fields are omitted. In the main, the selections have been culled from writings in the general field of so-called clinical medicine. Vaccination is not represented, and if ever a second edition appears it by all means should include Edward Jenner's classic account of allergy in smallpox and vaccinia, a pioneer description of allergy in infectious diseases. The recent descriptions by physicians of undulant fever, Rocky Mountain spotted fever and tularemia also should receive consideration. The book is divided into ten sections: infectious diseases, diseases of metabolism, lead poisoning, diseases of the circulatory system, diseases of the blood, renal diseases, respiratory diseases, deficiency diseases, allergic diseases and diseases of the digestive tract. Except when otherwise indicated, the editor is responsible for the translations into English. This book will have a special appeal to physicians who are interested in the historical development of the knowledge of disease, and it should be made easily available for students of medicine because it provides direct and stimulating contact with the founders of nosography.

The Wisdom of the Body. By Walter B. Cannon, M.D., Sc.D., LL.D., George Higginson, Professor of Physiology, Harvard Medical School. Price, $3.50. Pp. 312. New York: W. W. Norton & Company, Inc., 1932.

With this volume, the author enters the quasi-popular field. The essence of the subject matter is contained in a word of the author's coinage, "homeostasis," a term by which he designates the processes that preserve physiologic stability in the living organism. From the large number of such forms of "homeostasis," those selected for detailed discussion are the ones with which the author has been most intimately concerned, namely, those related to the functions of the "sympathico-adrenal" mechanism. Thus, hunger, thirst, hemorrhage and shock, the fluctuations in blood sugar and certain aspects of the physiology of respiration receive emphasis, while other processes, for example the responses of the body to the challenges of invading micro-organisms, are much more briefly dealt with.

Professor Cannon's book enjoys the distinction of few works of the kind in being doubly authoritative. The distinguished position of the author in the scientific world might have permitted him to present many concepts *ex cathedra* without detracting from the value of the work so far as the average lay reader is concerned. The author has not relied on such a method. For the most part, he has followed the manner of the technical journals, citing previous experimenters by name and describing in detail many of his own researches, before stating conclusions. Whether or not he has thus fully succeeded in presenting the material in a manner intelligible to "anyone who has had a simple training in biology and in general science" must remain for each reader to determine. Since writers on popular science have so frequently been lured away from strict facts by the

temptation to dramatize their subject, discerning readers have in this book an opportunity for unusual satisfaction and refreshment. The numerous charts are helpful. Each chapter is followed by a short bibliography, and there is appended a list of the publications of the author and his co-workers and pupils on which the book is based.

Vitamins: A Survey of Present Knowledge. Compiled by a Committee appointed jointly by the Lister Institute and Medical Research Council. Medical Research Council, Special Report Series No. 167. Price, 6 shillings, 6 pence, net. Pp. 319. London: His Majesty's Stationery Office, 1932. (Can be obtained from The British Library of Information, 5, East Forty-Fifth Street, New York.)

This book is the third edition of a report about the knowledge concerning vitamins by a committee of the Medical Research Council published in 1919. The survey now presented "is an entirely fresh resumption of current knowledge and of technical methods in this subject." The committee in charge of the survey is composed of leading English workers in the vitamin field, under the chairmanship of E. Mellanby. The general editor is Arthur Harden. An enumeration of the chapter headings will indicate the scope of the report: historical introduction; the fat-soluble vitamins, vitamin A; vitamin D (the antirachitic, calcifying vitamin); vitamins and dental tissues; vitamin E; the vitamin B complex; pellagra as a vitamin deficiency disease; vitamin C, the antiscorbutic vitamin; some nutritional aspects of cow's milk with special reference to vitamins; vitamins and human diets; vitamins in relation to the diet of the mother and the infant. The references, arranged alphabetically according to authors, cover about twenty-five pages. The titles to articles in periodicals are omitted, which will please those interested in the economics of scientific printing. Appendix 1 consists of a table giving the distribution of vitamins in foodstuffs. Appendix 2 contains a report of the conference on vitamin standards in London in June, 1931. At the end is a complete index. The survey as a whole is an admirable and complete summary of the development and present state of knowledge of the vitamins. The historical introduction and historical summaries elsewhere are models of their kind. The survey will be of great help to students in the vitamin field everywhere. Its manifest usefulness should tend to overthrow the statement in the preface that further revising may not be justifiable. It is hard to believe that the publication as proposed of a new journal, *Nutrition Abstracts and Reviews,* will meet fully the need for systematic and comprehensive summaries of the order of this survey.

The Sputum: Its Examination and Clinical Significance. By Randall Clifford, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School. Price, $4. Pp. 167, with 21 figures and 7 plates in colors. New York: The Macmillan Company, 1932.

This book is offered as a practical guide in the examination of the sputum and in the clinical interpretation of the results. It aims to meet the needs of physicians and medical students in their own work. There are four sections. The first deals with the sputum in general and with practical points in its collection. The second section describes macroscopic examination: physical characteristics, gross constituents and chemical features. The third section deals with microscopic examination: the unstained smear, the Ziehl-Neelsen method of staining for tubercle bacilli, Smith's gram-eosin stain and the Fontana stain. In the fourth section the character and clinical significance of the sputum in common diseases of the bronchi and lungs is discussed. The illustrations, twenty-one in black and white and seven in colors, are appropriate and helpful. The book is an authoritative guide to the microscopic examination of the sputum for clinical purposes.

Books Received

HANDBUCH DER BLUTGRUPPENKUNDE. Bearbeitet von Dr. H. Bürkle-de la Camp, Privatdozent, Oberarzt der chirurgischen Universitätsklinik München; Dr. M. Hesch, Assistent am anthropologisch-ethnologischen Forschungsinstitut der Universität Leipzig; Dr. G. Raestrup, o. Professor, Direktor des Instituts für gerichtliche Medizin der Universität, Frankfurt a. M.; Dr. E. D. Schött, Facharzt für Haut- und Geschlechtskrankheiten; Dr. P. Steffan, Marinegeneraloberarzt, Chefarzt des Marine-lazaretts, Wilhelmshaven; Dr. O. Thomsen, o. Professor, Direktor des Instituts für allgemeine Pathologie, Kopenhagen; I. S. Wellisch, Senatsrat, Wien. Herausgegeben von Dr. Paul Steffan, Marinegeneraloberarzt und Chefarzt des Marine-lazaretts, Wilhelmshaven. Mit 125 Abbildungen und 3 Karten. Price, paper, 48 marks; bound, 50 marks. Munich: J. F. Lehmann, 1932.

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